ATTORNEY DOCKET NO. 600-69-CIP **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	
Jayasree Vaseduvan	Examiner: Amy Lewis Group Art Unit: 1614
Serial No.: 10/656,715	Anaheim, California
Filed: September 05, 2003	
For: COMPOSITIONS AND METHODS USING COMPOUNDS HAVING CYTOCHROME P450RAI INHIBITORY ACTIVITY CO-ADMINISTERED WITH VITAMIN A	

Certificate of Mailing

I hereby certify that this correspondence is being deposited on 2.6.06 with the United States Postal Service as first class mail in an envelope addressed to Mail Stop Non-Fee Amendment Commissioner of Patents, P.O. Box 1450, Alexandria Virginia, 22313-1450

Toni Whyte

Toni Whyte

February 6, 2006

Date

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

Honorable Commissioner
Alexandria, Virginia

Dear Sir:

02/09/2006 MBIZUNES 00000001 10656715

01 FC:1814 130.00 OP

Petitioner, ALLERGAN, INC., is the owner of one-hundred percent (100%) interest in the instant application. A copy of the assignment from the original inventor(s) to Petitioner of the instant application is submitted herewith. Said assignment is recorded on Reel/Frame 013886/0080 in the Patent Office assignment records. Petitioner hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 6,740,676. A copy of the assignment from the previous patent owner to Petitioner of Application Serial Number 10/100,638 filed on March 19, 2002 now United States Patent No. 6,740,676 is submitted herewith. The latter assignment is recorded on Reel/Frames 013898/0170 in the Patent Office's assignment records. Petitioner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, petitioner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned (whole title is supplied below) is empowered to act on behalf of the organization.

I have reviewed the assignment documents mentioned above and I certify that to the best of my knowledge title to the instant application and to prior Patent No. 6,740,676 is in Petitioner.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United Stated Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: February 2, 2006

Gabor L. Szekeres
Registration No. 28,675
attorney of record

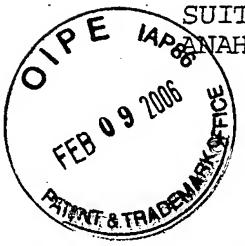
UNITED STATES
PATENT AND
TRADEMARK OFFICE

AUGUST 20, 2003

PTAS

Under Secretary of Commerce For Intellectual Property and
Director of the United States Patent and Trademark Office
Washington, DC 20231
www.uspto.gov

GABOR L. SZEKERES
8141 E. KAISER BLVD.
SUITE 112
ANAHEIM HILLS, CA 92808



UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 03/14/2003

REEL/FRAME: 013886/0080
NUMBER OF PAGES: 8

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
VASUDEVAN, JAYASREE
DOC DATE: 03/13/2003

ASSIGNOR:
WANG, LIMING
DOC DATE: 03/13/2003

ASSIGNOR:
LIU, XIAOXIA
DOC DATE: 03/13/2003

ASSIGNOR:
TSANG, KWOK-YIN
DOC DATE: 03/13/2003

ASSIGNOR:
YUAN, TANG-DAR
DOC DATE: 03/13/2003

ASSIGNOR:
CHANDRARATNA, ROSHANTHA A.
DOC DATE: 03/13/2003

ASSIGNEE:
ALLERGAN, INC.
2525 DUPONT DRIVE
IRVINE, CALIFORNIA 92612

SERIAL NUMBER: 10389071
PATENT NUMBER:

FILING DATE: 03/14/2003
ISSUE DATE:

LAZENA MARTIN, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

03-28-2003

102403545

Form PTO-1595
(Rev. 03/01)
OMB No. 0651-0027 (exp. 5/31/2002)

RECORDATION FORM COVER SHEET

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

Tab settings ⇨ ⇨ ⇨

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Jayasree Vasudevan
Liming Wang
Xiaoxia Liu
Kwok-Yin Tsang
Tang-Dar Yuan
Roshantha A. Chandraratna

03/14/03

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: ALLERGAN, Inc.

Internal Address:

Street Address: 2525 Dupont Drive

City: Irvine State: CA Zip: 92612

Additional name(s) & address(es) attached? ☐ Yes ☐ No

1135 U.S. PTO
10/389071
03/14/03

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other

Execution Date

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☐ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Gabor L. Szekeres

Internal Address:

Street Address: 8141 E. Kaiser Blvd.

Suite 112

City: Anaheim Hills State: CA Zip: 92808

6. Total number of applications and patents involved:

7. Total fee (37 CFR 3.41) $40.00

☐ Enclosed

☒ Authorized to be charged to deposit account

8. Deposit account number:

01-0885

(Attach duplicate copy of this page if paying by deposit account)

DO NO USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Gabor L. Szekeres — Name of Person Signing

Gabor L. Szekeres — Signature

March 14, 03 — Date

Total number of pages including cover sheet, attachments, and documents: 8

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

03/27/2003 TDIAZ1 00000190 010885 10389071
01 FC:8021 40.00 CH

ASSIGNMENT

WHEREAS, Jayasree VASUDEVAN, a citizen of India residing at 1220 S. Night Star Way, Anaheim, California 92808; **Liming WANG**, a citizen of the United States residing at 24 Del Ventura, Irvine, California 92606; **Xiaoxia LIU**, a citizen of the United States, residing at 1342 Walnut Ave., No. 103, Tustin, California 92780; **Kwok-Yin TSANG**, a citizen of Hong Kong residing at 1 Pollena, Irvine, California 92602; **Yang-Dar YUAN**, a citizen of the United States residing at 19212 Sierra Isabella, Irvine, California 92612; and **Roshantha A. CHANDRARATNA**, a citizen of the United States residing at 25241 Buckskin, Laguna Hills, California 92653; respectively (hereinafter referred to as **ASSIGNORS**), are co-inventors of a certain invention entitled: **4-[(8-SUBSTITUTED)-6-CHROMANOYL]- AND 4-[8-SUBSTITUTED)-CHROMAN-6-YL-ETHYNYL]-BENZOIC AND PHENYLACETIC ACKDS, THEIR ESTERS AND SALTS HAVING CYTOCHROME P450RAI INHIBITORY ACTIVITY** for which an application for Letters Patent of the United States was executed on even date herewith.

WHEREAS, ALLERGAN, INC., a California corporation having a place of business at 2525 Dupont Drive, Irvine, California 92612, United States of America (hereinafter referred to as **ASSIGNEE**), is desirous of acquiring the entire right, title and interest in, to and under said invention and in, to and under Letters Patent or similar legal protection to be obtained therefore in the United States and in any and all foreign countries.

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by **ASSIGNEE** to **ASSIGNORS** of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, **ASSIGNORS** hereby sell, assign and transfer to **ASSIGNEE** their entire right, title and interest to said Application and to the invention disclosed therein in the United States and its territorial possessions and in the foreign countries and to all Letters Patent or similar legal protection in the United States and its territorial possessions and in any and all foreign countries to be obtained for said invention by a subsequent utility patent application or any continuation, continuation-in-part, division, renewal, substitute or reissue thereof or any legal equivalent thereof in any foreign country for the full term or terms for which the same may be granted, and all rights of priority under International Conventions and applications for Letters Patent which may hereafter be filed for said invention in any country or countries foreign to the United States, and all Letters Patent which may be granted for said invention in any country or countries foreign to the United States and all extensions, renewals, and reissues thereof; and **ASSIGNORS** hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said invention to **ASSIGNEE**.

ASSIGNORS hereby covenant that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale;

ASSIGNORS further covenant that **ASSIGNEE** will, upon its request, be provided promptly with all pertinent facts and documents relating to said application, said invention and said Letters Patent and legal equivalents in foreign countries as may be known and accessible to **ASSIGNORS** and will testify as to the same in any interference or litigation

related thereto and will promptly execute and deliver to **ASSIGNEE** or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof in the United States of America and in any foreign country which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I have hereunto set hand and seal this 13th day of March, 2003.

Jayasree Vasudevan

Jayasree Vasudevan

State of California)
) ss.:
County of Orange)

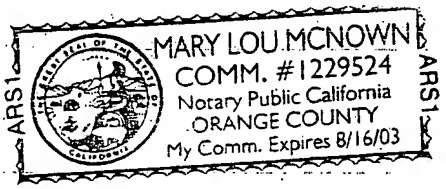
On this 13th day of MARCH, 2003, before me, Mary Lou McNown a Notary Public in and for the State and County aforesaid, personally appeared Jayasree Vasudevan proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that she executed the same in her authorized capacity, and that by her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal:

Mary Lou McNown

Notary Public

SEAL:



IN WITNESS WHEREOF, I have hereunto set hand and seal this 13 day of March, 2003.

Liming Wang

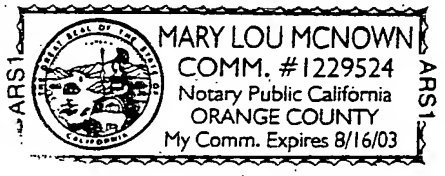
State of California)
) ss.:
County of Orange)
)

On this 13th day of MARCH, 2003, before me, Mary Lou McNown a Notary Public in and for the State and County aforesaid, personally appeared Liming Wang proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that she executed the same in her authorized capacity, and that by her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal:

Notary Public

SEAL:



IN WITNESS WHEREOF, I have hereunto set hand and seal this 13th day of March, 2003.

Xiaoxia Liu

State of California)
) ss.:
County of Orange)
)

On this 13th day of MARCH, 2003, before me, Mary Lou McNown a Notary Public in and for the State and County aforesaid, personally appeared Xiaoxia Liu proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that she executed the same in his authorized capacity, and that by ~~his~~ her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal:

Notary Public

SEAL:

MARY LOU MCNOWN
COMM. #1229524
Notary Public California
ORANGE COUNTY
My Comm. Expires 8/16/03

IN WITNESS WHEREOF, I have hereunto set hand and seal this
March 13 day of March, 2003.

Kwok-Yin Tsang

State of California)
) ss.:
County of Orange)
)

On this 13th day of MARCH, 2003, before me, Mary Lou McNown a Notary Public in and for the State and County aforesaid, personally appeared Kwok-Yin Tsang proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

Mary Lou McNown
Notary Public

SEAL:

IN WITNESS WHEREOF, I have hereunto set hand and seal this 13 day of March, 2003.

Yang-Dar YUAN

State of California)
) ss.:
County of Orange)

On this 13th day of MARCH, 2003, before me, Mary Lou McNown a Notary Public in and for the State and County aforesaid, personally appeared Yang-Dar Yuan proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that ~~he~~ she executed the same in ~~his~~ her authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

Notary Public

SEAL:

MARY LOU MCNOWN
COMM. #1229524
Notary Public California
ORANGE COUNTY
My Comm. Expires 8/16/03

IN WITNESS WHEREOF, I have hereunto set hand and seal this 13th day of March, 2003.

Roshantha A. Chandraratna

Roshantha A. Chandraratna

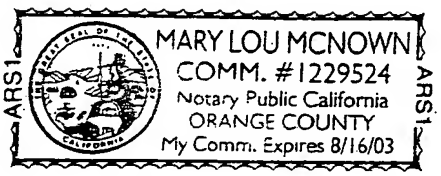
State of California)
) ss.:
County of Orange)
)

On this 13th day of MARCH, 2003, before me, Mary Lou McNown a Notary Public in and for the State and County aforesaid, personally appeared Roshantha A. Chandraratna proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

Mary Lou McNown

Notary Public

SEAL:



UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

JUNE 21, 2004

PTAS

102617533A

GABOR L. SZEKERES
8141 E. KAISER BLVD.
SUITE 112
ANAHEIM, CA 92808

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 12/04/2003

REEL/FRAME: 014752/0528
NUMBER OF PAGES: 6

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
YUAN, YANG-DAR — DOC DATE: 09/19/2003

ASSIGNOR:
VASUDEVAN, JAYASREE — DOC DATE: 09/19/2003

ASSIGNOR:
THACHER, SCOTT — DOC DATE: 09/18/2003

ASSIGNOR:
CHANDRARATNA, ROSHANTHA A. — DOC DATE: 09/19/2003

ASSIGNEE:
ALLERGAN, INC.
2525 DUPONT DRIVE
IRVINE, CALIFORNIA 92612

SERIAL NUMBER: 10656715 FILING DATE: 09/05/2003
PATENT NUMBER: ISSUE DATE:
TITLE: COMPOSITIONS AND METHODS USING COMPOUNDS HAVING CYTOCHROME P450RAI INHIBITORY ACTIVITY CO-ADMINISTERED WITH VITAMIN A

SHARON LATIMER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

12-08-2003

102617533

Form PTO-1595
(Rev. 03/01)
OMB No. 0651-0027 (exp. 5/31/2002)

RECORDA

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U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

Tab settings ⇨ ⇨ ⇨ 12.4.03

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Yang-Dar YUAN
Jayasree VASUDEVAN
Scott THACHER
Roshantha A. CHANDRARATNA

Additional name(s) of conveying party(ies) attached? ☐ Yes ☐ No

2. Name and address of receiving party(ies)

Name: ALLERGAN, INC.

Internal Address:

Street Address: 2525 Dupont Drive

City: Irvine State: California Zip: 92612

Additional name(s) & address(es) attached? ☐ Yes ☒ No

2003 DEC -4 AM 9:10
OFFICE OF PUBLIC RECORDS
FINANCE SECTION

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other

Execution Date

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
10/656,715 Filed on September 5, 2003

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Gabor L. Szekeres

Internal Address: Suite 112

Street Address: 8141 E. Kaiser Blvd.

City: Anaheim State: CA Zip: 92808

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $40.00

☒ Enclosed

☐ Authorized to be charged to deposit account

8. Deposit account number: Please apply any deficiencies to the deposit account listed below:

502362

(Attach duplicate copy of this page if paying by deposit account)

12/05/2003 DBYRNE 00000039 10656715
01 FC:8021 40.00 OP

DO NO USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Gabor L. Szekeres — Name of Person Signing

Gabor L. Szekeres — Signature

December 2, 03 — Date

Total number of pages including cover sheet, attachments, and documents: 7

Mail documents to be recorded with required cover sheet information to:
Mail Stop Assignment Recordation Services, Director of the US Patent and Trademark Office, PO Box 1450, Alexandria VA 22313-1450

ATTORNEY DOCKET NO. 600-69-PA PATENT

ASSIGNMENT

WHEREAS, Yang-Dar Yuan, a citizen of the United States of America, residing at 19212 Sierra Isabella Road, Irvine, California 92612-3936 US; Jayasree Vasudevan, a citizen of India, residing at 1220 South Night Starway, Anaheim, California 92808 US; Scott Thacher, a citizen of the United States of America, residing at 2692 Redlands Drive, Costa Mesa, California 92627 US; Roshantha A. Chandraratna, a citizen of the United States of America, residing at 25241 Buckskin Drive, Laguna Hills, California 92653-5736 US; respectively (hereinafter referred to as **ASSIGNORS**), are co-inventors of a certain invention entitled: **COMPOSITIONS AND METHODS USING COMPOUNDS HAVING CYTOCHROME P450RAI INHIBITORY ACTIVITY COADMINISTERED WITH VITAMIN A** for which an application for Letters Patent of the United States was filed on September 5, 2003, and has serial number 10/656,715.

WHEREAS, ALLERGAN, INC., a Delaware corporation having a place of business at 2525 Dupont Drive, Irvine, California 92612, United States of America (hereinafter referred to as **ASSIGNEE**), is desirous of acquiring the entire right, title and interest in, to and under said invention and in, to and under Letters Patent or similar legal protection to be obtained therefore in the United States and in any and all foreign countries.

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by **ASSIGNEE** to **ASSIGNORS** of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, **ASSIGNORS** hereby sell, assign and transfer to **ASSIGNEE** their entire right, title and interest to said Application and to the invention disclosed therein in the United States and its territorial possessions and in the foreign countries and to all Letters Patent or similar legal protection in the United States and its territorial possessions and in any and all foreign countries to be obtained for said invention by a subsequent utility patent application or any continuation, continuation-in-part, division, renewal, substitute or reissue thereof or any legal equivalent thereof in any foreign country for the full term or terms for which the same may be granted, and all rights of priority under International Conventions and applications for Letters Patent which may hereafter be filed for said invention in any country or countries foreign to the United States, and all Letters Patent which may be granted for said invention in any country or countries foreign to the United States and all extensions, renewals, and reissues thereof; and **ASSIGNORS** hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said invention to **ASSIGNEE**.

ASSIGNORS hereby covenant that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale;

ASSIGNORS further covenant that **ASSIGNEE** will, upon its request, be provided promptly with all pertinent facts and documents relating to said application, said invention and said Letters Patent and legal equivalents in foreign countries as may be known and accessible to

ASSIGNORS and will testify as to the same in any interference or litigation related thereto and will promptly execute and deliver to **ASSIGNEE** or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof in the United States of America and in any foreign country which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I have hereunto set hand and seal this 19th day of September, 2003.

Yang-Dar Yuan

State of California)
) ss.:
County of Orange)

Tamara J. Hallen

On this 19th day of September, 2003, before me, ~~Mary Lou McNown~~ a Notary Public in and for the State and County aforesaid, personally appeared Yang-Dar Yuan, proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument, the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal:

~~Mary Lou McNown~~, Notary Public
Tamara J. Hallen

SEAL:

TAMARA J. HALLEN
Commission # 1414872
Notary Public - California
Orange County
My Comm. Expires May 29, 2007

IN WITNESS WHEREOF, I have hereunto set hand and seal this 19th day of September, 2003.

Jayasree Vasudevan

Jayasree Vasudevan

State of California)
) ss.:
County of Orange)

Tamara J. Hallen

On this 19th day of September, 2003, before me, ~~Mary Lou McNown~~ a Notary Public in and for the State and County aforesaid, personally appeared Jayasree Vasudevan, proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that she executed the same in her authorized capacity, and that by her signature on the instrument, the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal:

~~Mary Lou McNown~~, Notary Public
Tamara J. Hallen

SEAL:

TAMARA J. HALLEN
Commission # 1414872
Notary Public - California
Orange County
My Comm. Expires May 29, 2007

IN WITNESS WHEREOF, I have hereunto set hand and seal this 18th day of September, 2003.

Scott Thacher

Scott Thacher

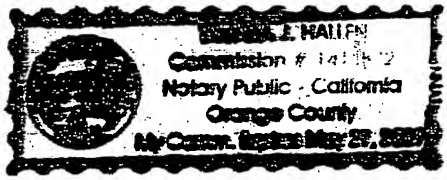
State of California)
) ss.:
County of Orange)

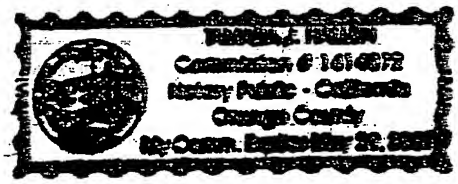
On this 18th day of September, 2003, before me, a Notary Public in and for the State and County aforesaid, personally appeared Scott Thacher proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal:

Notary Public

SEAL:





IN WITNESS WHEREOF, I have hereunto set hand and seal this 19th day of September, 2003.

Roshantha A. Chandraratna

Roshantha A. Chandraratna

State of California)
) ss.:
County of Orange)

On this 19th day of September, 2003, before me, ~~Mary Lou McNown~~ Tamara J. Hallen a Notary Public in and for the State and County aforesaid, personally appeared Roshantha A. Chandraratna proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that she executed the same in her authorized capacity, and that by her signature on the instrument, the person, or the entity upon behalf of which the person acted, executed the instrument.

Tamara J. Hallen

~~Mary Lou McNown~~, Notary Public
Tamara J. Hallen

SEAL:

TAMARA J. HALLEN
Commission # 1414672
Notary Public - California
Orange County
My Comm. Expires May 29, 2007

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

JUNE 21, 2004

PTAS

102617533A

GABOR L. SZEKERES
8141 E. KAISER BLVD.
SUITE 112
ANAHEIM, CA 92808

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 12/04/2003

REEL/FRAME: 014752/0528
NUMBER OF PAGES: 6

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
YUAN, YANG-DAR

DOC DATE: 09/19/2003

ASSIGNOR:
VASUDEVAN, JAYASREE

DOC DATE: 09/19/2003

ASSIGNOR:
THACHER, SCOTT

DOC DATE: 09/18/2003

ASSIGNOR:
CHANDRARATNA, ROSHANTHA A.

DOC DATE: 09/19/2003

ASSIGNEE:
ALLERGAN, INC.
2525 DUPONT DRIVE
IRVINE, CALIFORNIA 92612

SERIAL NUMBER: 10656715 FILING DATE: 09/05/2003
PATENT NUMBER: ISSUE DATE:
TITLE: COMPOSITIONS AND METHODS USING COMPOUNDS HAVING CYTOCHROME P450RAI INHIBITORY ACTIVITY CO-ADMINISTERED WITH VITAMIN A

SHARON LATIMER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

12-08-2003

102617533

Form PTO-1595
(Rev. 03/01)
OMB No. 0651-0027 (exp. 5/31/2002)

RECORDA

P

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

Tab settings ⇨ ⇨ ⇨ 12.4.03

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Yang-Dar YUAN
Jayasree VASUDEVAN
Scott THACHER
Roshantha A. CHANDRARATNA

Additional name(s) of conveying party(ies) attached? ☐ Yes ☐ No

2. Name and address of receiving party(ies)

Name: ALLERGAN, INC.

Internal Address: _____

Street Address: 2525 Dupont Drive

City: Irvine State: California Zip: 92612

Additional name(s) & address(es) attached? ☐ Yes ☒ No

03 DEC -4 AM 9:10
OFFICE OF PATENTS AND TRADEMARKS
FINANCE SECTION

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date _____

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: ____

A. Patent Application No.(s)
10/656,715 Filed on September 5, 2003

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Gabor L. Szekeres

Internal Address: Suite 112

Street Address: 8141 E. Kaiser Blvd.

City: Anaheim State: CA Zip: 92808

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $40.00

☒ Enclosed

☐ Authorized to be charged to deposit account

8. Deposit account number: Please apply any deficiencies to the deposit account listed below:

502362

(Attach duplicate copy of this page if paying by deposit account)

12/05/2003 DBYRNE 00000039 10656715
01 FC:8021 40.00 DP

DO NO USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Gabor L. Szekeres
Name of Person Signing

Gabor L. Szekeres
Signature

December 2, 03
Date

Total number of pages including cover sheet, attachments, and documents: 7

Mail documents to be recorded with required cover sheet information to:
Mail Stop Assignment Recordation Services, Director of the US Patent and Trademark Office, PO Box 1450, Alexandria VA 22313-1450

ATTORNEY DOCKET NO. 600-69-PA PATENT

ASSIGNMENT

WHEREAS, Yang-Dar Yuan, a citizen of the United States of America, residing at 19212 Sierra Isabella Road, Irvine, California 92612-3936 US; Jayasree Vasudevan, a citizen of India, residing at 1220 South Night Starway, Anaheim, California 92808 US; Scott Thacher, a citizen of the United States of America, residing at 2692 Redlands Drive, Costa Mesa, California 92627 US; Roshantha A. Chandraratna, a citizen of the United States of America, residing at 25241 Buckskin Drive, Laguna Hills, California 92653-5736 US; respectively (hereinafter referred to as **ASSIGNORS**), are co-inventors of a certain invention entitled: **COMPOSITIONS AND METHODS USING COMPOUNDS HAVING CYTOCHROME P450RAI INHIBITORY ACTIVITY COADMINISTERED WITH VITAMIN A** for which an application for Letters Patent of the United States was filed on September 5, 2003, and has serial number 10/656,715.

WHEREAS, ALLERGAN, INC., a Delaware corporation having a place of business at 2525 Dupont Drive, Irvine, California 92612, United States of America (hereinafter referred to as **ASSIGNEE**), is desirous of acquiring the entire right, title and interest in, to and under said invention and in, to and under Letters Patent or similar legal protection to be obtained therefore in the United States and in any and all foreign countries.

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by **ASSIGNEE** to **ASSIGNORS** of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, **ASSIGNORS** hereby sell, assign and transfer to **ASSIGNEE** their entire right, title and interest to said Application and to the invention disclosed therein in the United States and its territorial possessions and in the foreign countries and to all Letters Patent or similar legal protection in the United States and its territorial possessions and in any and all foreign countries to be obtained for said invention by a subsequent utility patent application or any continuation, continuation-in-part, division, renewal, substitute or reissue thereof or any legal equivalent thereof in any foreign country for the full term or terms for which the same may be granted, and all rights of priority under International Conventions and applications for Letters Patent which may hereafter be filed for said invention in any country or countries foreign to the United States, and all Letters Patent which may be granted for said invention in any country or countries foreign to the United States and all extensions, renewals, and reissues thereof; and **ASSIGNORS** hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said invention to **ASSIGNEE**.

ASSIGNORS hereby covenant that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale;

ASSIGNORS further covenant that **ASSIGNEE** will, upon its request, be provided promptly with all pertinent facts and documents relating to said application, said invention and said Letters Patent and legal equivalents in foreign countries as may be known and accessible to

ASSIGNORS and will testify as to the same in any interference or litigation related thereto and will promptly execute and deliver to **ASSIGNEE** or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof in the United States of America and in any foreign country which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I have hereunto set hand and seal this 19th day of September, 2003.

Yang-Dar Yuan

State of California)
) ss.:
County of Orange)

Tamara J. Hallen

On this 19th day of September, 2003, before me, ~~Mary Lou McNown~~, a Notary Public in and for the State and County aforesaid, personally appeared Yang-Dar Yuan, proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument, the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal:

~~Mary Lou McNown~~, Notary Public
Tamara J. Hallen

SEAL:

TAMARA J. HALLEN
Commission # 1414872
Notary Public - California
Orange County
My Comm. Expires May 29, 2007

IN WITNESS WHEREOF, I have hereunto set hand and seal this 19th day of September, 2003.

Jayasree Vasudevan

Jayasree Vasudevan

State of California)
) ss.:
County of Orange)

Tamara J. Hellen

On this 19th day of September, 2003, before me, ~~Mary Lou McNown~~ a Notary Public in and for the State and County aforesaid, personally appeared Jayasree Vasudevan, proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that she executed the same in her authorized capacity, and that by her signature on the instrument, the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal:

~~Mary Lou McNown~~, Notary Public
Tamara J. Hellen

SEAL:

TAMARA J. HALLEN
Commission # 1414672
Notary Public - California
Orange County
My Comm. Expires May 29, 2007

IN WITNESS WHEREOF, I have hereunto set hand and seal this 18th day of September, 2003.

Scott Thacher

Scott Thacher

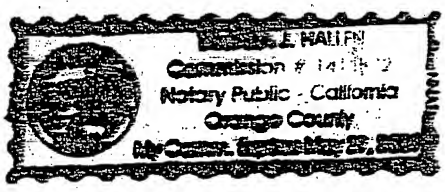
State of California)
) ss.:
County of Orange)

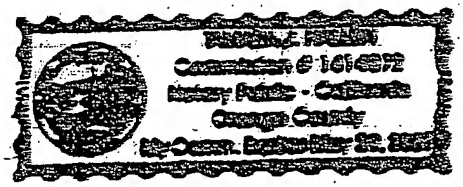
On this 18th day of September, 2003, before me, a Notary Public in and for the State and County aforesaid, personally appeared Scott Thacher proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal:

Notary Public

SEAL:





IN WITNESS WHEREOF, I have hereunto set hand and seal this 19th day of September, 2003.

Roshantha A. Chandraratna

Roshantha A. Chandraratna

State of California)
) ss.:
County of Orange)

Tamara J. Hallen

On this 19th day of September, 2003, before me, ~~Mary Lou McNown~~ a Notary Public in and for the State and County aforesaid, personally appeared Roshantha A. Chandraratna proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument, and acknowledged to me that she executed the same in her authorized capacity, and that by her signature on the instrument, the person, or the entity upon behalf of which the person acted, executed the instrument.

Tamara J. Hallen

~~Mary Lou McNown~~, Notary Public
Tamara J. Hallen

SEAL:

TAMARA J. HALLEN
Commission # 1414572
Notary Public - California
Orange County
My Comm. Expires May 29, 2007

UNITED STATES PATENT AND TRADEMARK OFFICE

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LEGAL/PATENTS

AUGUST 26, 2003

PTAS

Deputy Under Secretary of Commerce For Intellectual Property and
Deputy Director of the United States Patent and Trademark Office
Washington, DC 20231
www.uspto.gov

ALLERGAN, INC.
MARTIN A. VOET
2525 DUPONT DRIVE
IRVINE, CALIFORNIA 92612

102416576A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 04/07/2003

REEL/FRAME: 013898/0170
NUMBER OF PAGES: 17

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ALLERGAN SALES, INC. (MERGED INTO ALLERGAN SALES, LLC 6/3/2002)

DOC DATE: 03/31/2003

ASSIGNEE:
ALLERGAN, INC.
2525 DUPONT DRIVE
IRVINE, CALIFORNIA 92612

SERIAL NUMBER: 10104899
PATENT NUMBER:

FILING DATE: 03/22/2002
ISSUE DATE:

SERIAL NUMBER: 10008722
PATENT NUMBER:

FILING DATE: 12/06/2001
ISSUE DATE:

SERIAL NUMBER: 10365082
PATENT NUMBER:

FILING DATE: 02/11/2003
ISSUE DATE:

SERIAL NUMBER: 10108714
PATENT NUMBER:

FILING DATE: 03/28/2002
ISSUE DATE:

SERIAL NUMBER: 09903954	FILING DATE: 07/12/2001
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 09998358	FILING DATE: 11/29/2001
PATENT NUMBER: 6610744	ISSUE DATE: 08/26/2003
SERIAL NUMBER: 10017660	FILING DATE: 12/12/2001
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 10116492	FILING DATE: 04/03/2002
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 09367712	FILING DATE: 08/18/1999
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 09264531	FILING DATE: 03/08/1999
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 09329752	FILING DATE: 06/10/1999
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PATENT NUMBER:	ISSUE DATE:
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SERIAL NUMBER: 10099239 PATENT NUMBER:	FILING DATE: 03/15/2002 ISSUE DATE:
SERIAL NUMBER: 10099602 PATENT NUMBER:	FILING DATE: 03/14/2002 ISSUE DATE:
SERIAL NUMBER: 10143078 PATENT NUMBER:	FILING DATE: 05/10/2002 ISSUE DATE:

ALLYSON PURNELL, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

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04-11-2003

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4-7-03

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FINANCE SECTION

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LEGAL/PATENTS

To: The Commissioner of Patents and Trademarks,

Please record the attached original document(s) or copy(ies):

1. Submission Type:

X new

☐ Correction of PTO error (Reel /frame)

☐ Corrective Document (Reel /frame)

2. Conveyance Type:

X Assignment

☐ License

☐ Merger

☐ Security Agreement

☐ Change of Name

☐ Other: _____

3.

CONVEYING PARTIES	
Names of Conveying Parties	**Date of Conveyance**
1. Allergan Sales, Inc. (merged into Allergan Sales, LLC 6/3/2002)	March 31, 2003
2.	
3.	

☐ Additional Conveying Parties Attached

4.

RECEIVING PARTIES
Names of Receiving Parties
Name Allergan, Inc.
Address 1 2525 Dupont Drive
Address 2 Irvine, CA 92612

☐ Additional Receiving Parties Attached

☐ If document is an assignment and the Receiving Party is not domiciled in the United States, an appointment of a Domestic Representative is attached.

04/11/2003 ECOOPER 00000008 010885 10104899

01 FC:8021 4440.00 CH

5.

DOMESTIC REPRESENTATIVE NAME AND ADDRESS
Name
Address 1
Address 2

6.

CORRESPONDENCE NAME AND ADDRESS
Name Martin A. Voet (T2-7H)
Address 1 Allergan, Inc.
Address 2 2525 Dupont Drive, Irvine, CA 92612
Telephone 714-246-5894 and Fax 714-246-4249

7. Total Number of pages of the conveying document, including attachments: 17 pages

8.

APPLICATION NUMBER OR PATENT NUMBER (either; not both for same property)	
Application Number see attached Appendix A (3 pages)	Patent Number 10104899
Application Number	Patent Number

9. If this document is being filed with a NEW patent application, enter the Docket No., Title of the Invention, and date of execution of the Assignment by the first inventor:

Title of Patent Application: _____
Docket No.: _____
Date of Execution by First Inventor: _____

10. Total Number of Properties Involved: 111

11. The fee amount (37 CFR §3.41) of $ 4,440

X may be debited from our Deposit Account No. 01-0885.
☐ is enclosed as check no. _____.

12. X The Commissioner is authorized to deduct any additional fee amounts due in connection with the filing of this document from Deposit Account No. 01-0885.

To the best of my information and belief, all statements made herein are true, and any attached copy is a true copy of the original document.

Respectfully submitted,

SIGNATURE M A Voet Date: 4/2/2003
TYPED or PRINTED NAME: Martin A. Voet. REGISTRATION NO. 25,208

CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE WITH SUFFICIENT POSTAGE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: BOX ASSIGNMENT, COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231 ON April 2 2003 (Date)
Name of person making deposit: Mary Lou McNown
Signature: _____ Date _____

APPENDIX "A" (Page 1)

SERIAL NUMBER	INVENTORS	ALLERGAN NO.
10/104,899	Herbert K. Graham	16897-CIP
10/008,722	Aoki; et al.	16952-CON-DIV5-CIP
10/365,082	Aoki; et al.	16952-CON-DIV5-CIP-CON (BOT)
10/108,714	Regan; et al.	17023-DIV-CIP-CON
09/903,954	Michael E. Garst	17095-FWC-CIP-CON
09/998,358	Teng; et al.	17170-DIV2
10/017,660	Joseph S. Adorante	17219-CIP-CON3
10/116,492	Joseph S. Adorante	17219-CIP-CON4
09/367,712	John Sefton	17224
09/264,531	John Sefton	17235
not assigned	Olejnik; et al	17237-CON2-CIP-CON3
09/329,752	Chow; et al.	17243-CIP2
09/815,362	Chow; et al.	17243-CIP3
09/108,298	Nagpal; et al.	17253
09/294,980	Dolly; et al. **(only the portion assigned by Roger Aoki)**	17259
09/989,295	Beck; et al.	17273-CON
09/760,133	Firestone; et al.	17278-CON
09/288,326	Sachs; et al.	17282
09/548,409	Sachs; et al.	17282-CIP
10/304,665	Klein; et al.	17276-CIP-CON
09/919,195	Massaro; et al. **(only the portion assigned by Chandraratna)**	17293-DIV
10/305,049	Massaro; et al. **(only the portion assigned by Chandraratna)**	17294-CON
09/548,896	Chandraratna; et al. **(only the portion assigned by Chandraratna)**	17295
09/624,129	Muller; et al.	17300-CIP
09/838,772	Cheetham; et al.	17300-CIP2
10/236,712	Muller; et al.	17300-CIP-CON
10/194,834	Muller; et al.	17301-DIV2
09/590,447	Forman; et al. **(only that portion assigned by Beard and Chandraratna)**	17302
09/621,179	Chandraratna; et al.	17304
09/371,354	Stephen Donovan	17310
10/114,740	Gregory F. Brooks	17310-CIP
09/648,692	Dolly; et al.	17311
09/500,147	Terrence J. Hunt	17319
10/047,058	Terrence J. Hunt	17319-CIP
10/360,098	Terrence J. Hunt	17319-CIP-CIP

APPENDIX "A" (Page 2)

SERIAL NUMBER	INVENTORS	ALLERGAN NO.
10/135,595	Vasudevan; et al.	17321
10/038,215	Evan B. Dreyer	17322-CON
09/692,811	Stephen Donovan	17324
09/810,601	Stephen Donovan	17324-CIP
10/071,826	Donovan; et al.	17326-CIP2
09/552,823	Pacifici; et al.	17327-CIP
10/199,222	Aoki; et al.	17328-CON
09/489,667	Stephen Donovan	17329
09/938,112	Stephen Donovan	17329-DIV
09/625,098	Stephen Donovan	17329-CIP
10/039,520	Beard; et al.	17331-REF
09/533,680	Beard; et al.	17331
09/706,211	Stephen Donovan	17341-DIV
09/706,173	Stephen Donovan	17341-DIV2
09/706,172	Stephen Donovan	17341-DIV3
09/706,215	Stephen Donovan	17341-DIV5
10/017,834	Voet; et al.	17341-CIP2
10/099,238	Voet; et al.	17341-CIP3
09/704,464	Stephen Donovan	17342-DIV2
09/835,949	Stephen Donovan	17342-CON
09/971,869	Stephen Donovan	17342-DIV-CON
09/815,156	Klein; et al.	17346
09/850,835	Kusari; et al.	17347
09/548,315	Chow; et al.	17351
09/778,975	Chow; et al.	17351-CIP
09/561,106	Stephen Donovan	17354
09/904,018	Olejnik; et al.	17361
10/236,566	Olejnik; et al.	17361-CON
10/299,386	Olejnik; et al.	17361-DIV
10/146,224	Old; et al.	17366
10/300,492	Burk; et al.	17373-CON-CIP-CON
10/004,230	Steward; et al.	17376
09/640,852	Nehme; et al.	17377
09/651,235	Vasudevan; et al.	17379
10/079,993	Vasudevan; et al.	17382-DIV
10/364,225	Vasudevan; et al.	17382-DIV2
10/097,368	Vasudevan; et al.	17383-DIV
10/097,315	Vasudevan; et al.	17383-DIV2
10/212,533	Vasudevan; et al.	17386-DIV3
10/104,433	Burk; et al.	17390-CIP
09/847,935	Woodward; et al.	17392
10/155,925	Brooks; et al.	17396-CON
09/751,053	Gil; et al.	17399

SERIAL NUMBER	INVENTORS	ALLERGAN NO.
10/020,541	Wheeler; et al.	17400
09/998,718	Burke; et al.	17400-CIP
09/726,949	Lin; et al.	17408
10/051,952	Patricia S. Walker	17409-CIP
10/081,126	Gerald W. DeVries	17413
09/848,249	Woodward; et al.	17415
09/848,159	Yuan; et al.	17416
10/131,848	Huth; et al.	17421
09/814,604	Klein; et al.	17425
09/922,226	Zhao; et al.	17432
10/121,076	Robert T. Lyons	17433
09/882,720	Burk; et al.	17437
10/103,301	Burk; et al.	17437-CIP
10/346,828	Burk; et al.	17437-CON
10/294,521	Burk; et al.	17438-DIV
09/956,470	Liang; et al.	17440-CIP
09/918,847	Joshi; et al.	17442
09/904,753	Robert T. Lyons	17445
09/893,159	Woodward; et al.	17446
09/942,098	Steward; et al.	17451
09/942,024	Steward; et al.	17452
10/104,385	Forman; et al.	17453-CIP
09/954,610	Martin A. Voet	17455
10/143,076	Lam; et al.	17456
10/017,817	Chang; et al.	17462
10/016,850	Hughes; et al.	17468
10/016,036	David; et al. **(only that portion assigned by Robert David)**	17476
10/100,638	Vasudevan; et al.	17485
10/082,691	Stephen Donovan	17486
10/133,094	Stanley W. Huth	17487
10/099,239	Martin A. Voet	17489
10/099,602	Lisa D. Hanin	17493
10/143,078	Stephen Donovan	17500

ASSIGNMENT

WHEREAS: ALLERGAN, INC., a Delaware corporation, having its principal place of business at 2525 Dupont Drive, Irvine, California 92612 (hereinafter referred to as ASSIGNEE), is desirous of acquiring the entire right, title and interest in, to and under certain inventions and in, to and under corresponding Letters Patent or similar legal protection to be obtained therefor in the United States and in any and all foreign countries.

WHEREAS: On June 3, 2002, ALLERGAN SALES, INC., a California corporation, was merged into ALLERGAN SALES, LLC, a Delaware limited liability company pursuant to the "Agreement and Plan of Merger" filed with the Secretary of State of the State of California and with the Secretary of State of the State of Delaware (copy attached).

WHEREAS: ALLERGAN SALES, LLC, having its principal place of business at 2525 Dupont Drive, Irvine, California 92612 (hereinafter ASSIGNOR) by virtue of the above-mentioned merger owns the entire right, title and interest in, to and under certain inventions, corresponding U.S. patent applications and foreign rights directed thereto.

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by ASSIGNEE TO ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, ASSIGNOR hereby sells, assigns and transfers to ASSIGNEE the entire right, title and interest in, to and under certain inventions in the Untied States and its territorial possessions and in all foreign countries to all Letters Patents or similar legal protection in the United States and its territorial possessions and in any and all foreign countries to be obtained for certain inventions by certain applications set forth in Appendix "A" and any continuation, divisional, renewal, substitute or reissue thereof for the full term or

terms for which the same may be granted; said sale, transfer and assignment effective June 3, 2002.

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this 31 day of March 2003.

ALLERGAN SALES, LLC

By: Martin A. Voet
Martin A. Voet
Assistant Secretary

State of CALIFORNIA)
(ss.
County of ORANGE)

On March 31, 2003, before me, Mary Lou McNown, notary public, personally appeared MARTIN A. VOET personally known to me to be the person whose name is subscribed to the within instrument and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

Mary Lou McNown
Signature of Notary Public

678567

Merger Agreement

State of California

SECRETARY OF STATE

I, *BILL JONES*, Secretary of State of the State of California, hereby certify:

That the attached transcript of 6 page(s) has been compared with the record on file in this office, of which it purports to be a copy, and that it is full, true and correct.

IN WITNESS WHEREOF, I execute this certificate and affix the Great Seal of the State of California this day of

JUN 18 2002

Bill Jones

Secretary of State

Sec/State Form CE-107 (rev. 9/98)

OSP 98 13524

D0678567

ENDORSED - FILED
in the office of the Secretary of State
of the State of California

JUN - 3 2002

BILL JONES, Secretary of State

AGREEMENT AND PLAN OF MERGER

BETWEEN

ALLERGAN SALES, INC.
(a California corporation)

AND

ALLERGAN SALES, LLC
(a Delaware limited liability company)

THIS AGREEMENT AND PLAN OF MERGER is made as of June 3, 2002 (this "Agreement of Merger"), by and between Allergan Sales, Inc., a California corporation (the "Corporation"), and Allergan Sales, LLC, a Delaware limited liability company (the "LLC", and collectively with the Corporation the "Constituent Companies").

WHEREAS, the Corporation was incorporated by the filing of Articles of Incorporation with the Secretary of State of the State of California on March 20, 1980; and

WHEREAS, the LLC was formed by the filing of a Certificate of Formation with the Secretary of State of the State of Delaware on February 25, 2002, and Allergan, Inc., a Delaware corporation and the sole member of the LLC (the "Member"), has entered into a Limited Liability Company Agreement dated as of February 25, 2002 (the "Operating Agreement");

NOW, THEREFORE, the parties hereby agree as follows:

1. Upon the terms and subject to the conditions hereof and in accordance with the California General Corporation Law (the "CGCL") and the Delaware Limited Liability Company Act (the "DLLCA"), the Corporation shall be merged with and into the LLC (the "Merger") at the Effective Time (as hereinafter defined). Following the Merger, the separate existence of the Corporation shall cease, and the LLC shall continue as the surviving entity (the "Surviving Entity") and shall succeed to and assume all of the rights and obligations of the Corporation in accordance with the CGCL and the DLLCA.

2. The parties hereto shall cause the Merger to be consummated by filing this Agreement of Merger, along with a Certificate of Merger, with the Secretary of State of the State of California pursuant to Section 1113 of the CGCL, and by filing a Certificate of Merger (the "Certificate of Merger") with respect thereto with the Secretary of State of the State of Delaware pursuant to Section 18-209 of the DLLCA. When used in this Agreement of Merger, the term "Effective Date" shall mean the date of filing of the Certificate of Merger with the Secretary of State of the State of Delaware.

3. The Merger shall have the effects set forth in Section 1113(i) of the CGCL and Section 18-209(g) of the DLLCA. Without limiting the generality of the foregoing, and subject thereto, at the Effective Time, except as otherwise provided herein, all of the property,

rights, privileges, powers and franchises of the Corporation and the LLC shall rest in the Surviving Entity, and all debts, liabilities and duties of the Corporation and the LLC shall become the debts, liabilities and duties of the Surviving Entity.

4. As of the Effective Time, by virtue of the Merger and without any action on the part of the Member of the LLC, or the shareholders or the Board of Directors of the Corporation, each share of capital stock in the Corporation issued and outstanding immediately prior to the Effective Time shall be canceled and extinguished without consideration. The membership interests of the LLC outstanding immediately prior to the Effective Time shall continue to be outstanding and shall not be affected by the Merger.

5. If, at any time after the Effective Time, the Surviving Entity shall consider or be advised that any deeds, bills of sale, assignments or assurances or any other acts or things are necessary, desirable or proper (a) to vest, perfect or confirm, of record or otherwise, in the Surviving Entity, its right, title or interest in, to or under any of the rights, privileges, powers, franchises, properties or assets of either of the Constituent Companies, or (b) otherwise to carry out the purposes of this Agreement of Merger, the Surviving Entity and its proper authorized representatives shall be authorized to execute and deliver, in the name and on behalf of either of the Constituent Companies, all such deeds, bills of sale, assignments and assurances and do, in the name and on behalf of each of the Constituent Companies, all such other acts and things necessary, desirable or proper to vest, perfect or confirm its right, title or interest in, to or under any of the rights, privileges, powers, franchises, properties or assets of such constituent Company and otherwise to carry out the purposes of this Agreement of Merger.

6. As required by the CGCL, the Surviving Entity hereby agrees to (i) be served in the State of California in any proceeding for the enforcement of an obligation of any Constituent Company and in any proceeding to enforce the rights of any holder of a dissenting interest or dissenting shares in a constituent domestic limited liability company or domestic other business entity; (ii) irrevocably appoint the Secretary of State of the State of California as its agent for service of process, which process may be forwarded to 2525 Dupont Drive, Irvine, California 92612; and (iii) promptly pay the holder of any dissenting interest or dissenting share in a constituent domestic limited liability company or domestic other business entity the amount to which that person is entitled under California law.

IN WITNESS WHEREOF, the undersigned have caused this Agreement of Merger to be executed by their respective officers or representatives thereunto duly authorized as of the date first above written.

ALLERGAN SALES, INC.,
a California corporation

By: _____
Jeffrey L. Edwards
Vice President

By: _____
Matthew J. Maletta
Assistant Secretary

ALLERGAN SALES, LLC,
a Delaware limited liability company

By: ALLERGAN, INC., its Sole Member

By: _____

Name: Matthew J. Maletta

Title: Assistant Secretary

CERTIFICATE OF APPROVAL
OF
AGREEMENT AND PLAN OF MERGER

Jeffrey L. Edwards and Matthew J. Maletta state and certify that:

1. They are the Vice President and Assistant Secretary, respectively, of Allergan Sales, Inc., a California corporation.

2. The Agreement and Plan of Merger in the form attached was duly approved by the Board of Directors and the sole stockholder of the corporation.

3. There is only one class of shares and the total number of outstanding shares is 1,000 shares of Common Stock.

4. Approval of the Agreement and Plan of Merger by the holder of 100% of the outstanding shares of Common Stock was the vote required to approve the Agreement and Plan of Merger. The percentage of the outstanding shares of the corporation's shares entitled to vote on the Agreement of Merger which voted to approve the Agreement of Merger equaled the vote required.

5. No vote of the stockholders of the corporation's parent, Allergan, Inc., was required to approve the Agreement and Plan of Merger.

We further declare under penalty of perjury under the laws of the State of California that the matters set forth in this certificate are true and correct of our own knowledge.

Date: June 3, 2002

Jeffrey L. Edwards
Vice President

Matthew J. Maletta
Assistant Secretary

State of California
Bill Jones
Secretary of State

OTHER BUSINESS ENTITY CERTIFICATE OF MERGER

(Corporations Code Sections 1113(g)(1) and (2), 6019.1, 8019.1 and 12540.1)

Filing Fee – Please see instructions.

IMPORTANT – Read instructions before completing this form.

This Space For Filing Use Only

1. Name of surviving entity:	2. Type of entity:	3. Secretary of State File Number:	4. Jurisdiction:
Allergan Sales, LLC	LLC	200216110097	Delaware
5. Name of disappearing entity:	**6. Type of entity:**	**7. Secretary of State File Number:**	**8. Jurisdiction:**
Allergan Sales, Inc.	Corporation	C0978306	California

9. Future effective date, if any: Month Day Year

10. If a vote was required enter the outstanding interests of each class entitled to vote on the merger and the percentage of vote required:

Surviving Entity		Disappearing Entity	
Each class entitled to vote	Percentage of vote required	Each class entitled to vote	Percentage of vote required
Sole Member	100%	Sole Shareholder 1,000 common shares issued	100%

11. The principal terms of the agreement of merger were approved by a vote of the number of interests or shares of each class that equaled or exceeded the vote required.

12. If equity securities of a parent party are to be issued in the merger:
[ ] No vote of the shareholders of the parent party was required. [ ] The required vote of the shareholders of the parent party was obtained.

SECTION 13 IS ONLY APPLICABLE IF THE SURVIVING ENTITY IS A DOMESTIC LIMITED LIABILITY COMPANY, DOMESTIC LIMITED PARTNERSHIP OR PARTNERSHIP.

13. Requisite changes to the information set forth in the Articles of Organization, Certificate of Limited Partnership or Statement of Partnership Authority of the surviving limited liability company, limited partnership or partnership resulting from the merger. Attach additional pages, if necessary.

SECTION 14 IS APPLICABLE IF THE SURVIVING ENTITY IS AN OTHER BUSINESS ENTITY.

14. Principal business address of the surviving other business entity:
Address: 2525 Dupont Drive
City: Irvine State: California Zip: 92612

15. Other information required to be stated in the Certificate of Merger by the laws under which each constituent other business entity is organized. Attach additional pages if necessary.

16. Statutory or other basis under which each foreign other business entity is authorized to effect the merger:
Delaware Limited Liability Company Act Section 18-209

17. Number of pages attached, if any: 1

18. I certify that the statements contained in this document are true and correct of my own knowledge. I declare that I am the person who is executing this instrument, which execution is my act and deed.

See Attached Signature of Authorized Person for the Surviving Entity	Date	Type or Print Name and Title of Person Signing	Date
See Attached Signature of Authorized Person for the Surviving Entity	Date	Type or Print Name and Title of Person Signing	Date
See Attached Signature of Authorized Person for the Disappearing Entity	Date	Type or Print Name and Title of Person Signing	Date
See Attached Signature of Authorized Person for the Disappearing Entity	Date	Type or Print Name and Title of Person Signing	Date

For an entity that is a business trust, real estate investment trust or an unincorporated association, set forth the provision of law or other basis for the authority of the person signing.

ATTACHMENT PAGE
TO
OTHER BUSINESS ENTITY
CERTIFICATE OF MERGER

18. Signature of Authorized person for the Surviving Entity

Dated: June 3, 2002

ALLERGAN SALES, LLC,
a Delaware limited liability company

ALLERGAN, INC.,
a Delaware corporation,
its sole member

By: _____

Name: Matthew J. Maletta

Title: Assistant Secretary

Signature of Authorized person for the Disappearing Entity

Dated: June 3, 2002

ALLERGAN SALES, INC.,
a California corporation

By: _____

Name: Jeffrey L. Edwards

Title: Vice President

By: _____

Name: Matthew J. Maletta

Title: Assistant Secretary

OFFICE OF THE SECRETARY OF STATE

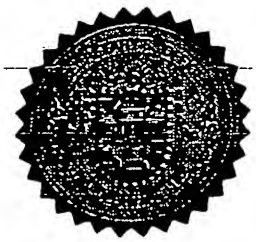
Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF MERGER, WHICH MERGES:

"ALLERGAN SALES, INC.", A CALIFORNIA CORPORATION,

WITH AND INTO "ALLERGAN SALES, LLC" UNDER THE NAME OF "ALLERGAN SALES, LLC", A LIMITED LIABILITY COMPANY ORGANIZED AND EXISTING UNDER THE LAWS OF THE STATE OF DELAWARE, AS RECEIVED AND FILED IN THIS OFFICE THE THIRD DAY OF JUNE, A.D. 2002, AT 9 O'CLOCK A.M.



Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

3496059 8100M

020354968

AUTHENTICATION: 1809761

DATE: 06-03-02

CERTIFICATE OF MERGER
OF
ALLERGAN SALES, INC.
(a California corporation)
WITH AND INTO
ALLERGAN SALES, LLC
(a Delaware limited liability company)

(Pursuant to Section 18-209 of the Delaware Limited Liability Company Act)

Pursuant to the provisions of Section 18-209 of the Delaware Limited Liability Company Act ("DLLCA"), the undersigned surviving limited liability company submits the following Certificate of Merger for filing and certifies that:

FIRST: The name and jurisdiction of formation or incorporation of the limited liability company and corporation which are parties to the merger (the "constituent entities") are as follows:

Name of Entity	State of Formation or Incorporation
Allergan Sales, Inc.	California
Allergan Sales, LLC	Delaware

SECOND: An Agreement and Plan of Merger (the "Merger Agreement") between the constituent entities has been approved and executed by each of the constituent entities which are to merge in accordance with the requirements of Section 18-209 of the DLLCA.

THIRD: The name of the surviving limited liability company is: Allergan Sales, LLC (the "Surviving Entity").

FOURTH: The merger shall become effective upon filing of this Certificate of Merger.

FIFTH: The executed Merger Agreement is on file at the office of the Surviving Entity, the address of which is 2525 Dupont Drive, Irvine, California 92612.

SIXTH: A copy of the Merger Agreement will be furnished by the Surviving Entity, on request and without cost, to any member of the Surviving Entity or to any person holding an interest in the entity which is to merge with and into the Surviving Entity.

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 09:00 AM 06/03/2002
020354968 – 3496059

IN WITNESS WHEREOF, this Certificate of Merger has been duly executed as of the 3rd day of June, 2002, and is being filed in accordance with Section 18-209 of the DLLCA by a duly authorized person on behalf of Allergan Sales, LLC.

ALLERGAN SALES, LLC,
a Delaware limited liability company

ALLERGAN, INC.,
a Delaware corporation,
its sole member

By: _____

Name: Matthew J. Maletta

Title: Assistant Secretary

USPTO PATENT FULL-TEXT AND IMAGE DATABASE

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Searching 1976 to present...

Results of Search in 1976 to present db for:
TTL/retinoid: 287 patents.
*Hits **1** through **50** out of **287***

Next 50 Hits

Jump To

Refine Search ttl/retinoid

	PAT. NO.	Title
1	6,992,108	Means for the modulation of processes mediated by retinoid receptors and compounds useful therefor
2	RE38,813	Retinoid compositions containing a water soluble antioxidant and a chelator
3	6,949,247	Stable skin care compositions containing a retinoid and a retinoid booster system
4	6,861,238	Retinoid metabolizing protein
5	6,858,647	Retinoid compounds suited for antibacterial applications
6	6,855,832	O- or S-substituted tetrahydronaphthalene derivatives having retinoid and/or retinoid antagonist-like biological activity
7	6,844,466	Alkyl urea retinoid agonists
8	6,844,364	Stabilization of retinoid compounds
9	6,838,472	Substituted urea retinoid agonists
10	6,838,442	Combination therapy comprising glucose reabsorption inhibitors and retinoid-X receptor modulators
11	6,828,337	Selective retinoid agonists
12	6,825,233	Compounds having retinoid-like activity
13	6,818,775	Alkyl or aryl substituted dihydronaphthalene derivatives having retinoid and/or retinoid antagonist-like biological activity
14	6,818,652	Heterocyclic retinoid compounds
15	6,777,418	Retinoid compounds (I)
16	6,759,396	Compositions based on a synergistic mixture of at least one VDR ligand and a retinoid
17	6,743,437	Implant device with a retinoid for improved biocompatibility
18	6,720,425	Alkyl or aryl substituted dihydronaphthalene derivatives having retinoid and/or retinoid antagonist-like biological activity

EXHIBIT 1

19 6,720,423 T Dihydrobenzofuran and dihydrobenzothiophene 2,4-pentadienoic acid derivatives having selective activity for retinoid X (RXR) receptors

20 6,660,755 T Substituted diaryl or diheteroaryl methans, ethers and amines having retinoid agonist, antagonist or inverse agonist type biological activity

21 6,653,483 T Alkyl or aryl substituted dihydronaphthalene derivatives having retinoid and/or retinoid antagonist-like biological activity

22 6,641,824 T Skin treatment using a new retinoid

23 6,638,543 T Use of natural EGFR inhibitors to prevent side effects due to retinoid therapy, soaps, and other stimuli that activate the epidermal growth factor receptor

24 6,627,652 T Method of treatment with compounds having selective agonist-like activity on RXR retinoid receptors

25 6,624,188 T Method of treatment with compounds having retinoid-like activity and reduced skin toxicity and lacking teratogenic effects

26 6,613,917 T Amines substituted with a dihydronaphthalenyl, chromenyl, or thiochromenyl group, an aryl or heteroaryl group and an alkyl group, having retinoid-like biological activity

27 6,610,883 T Compounds having selective activity for retinoid X receptors, and means for modulation of processes mediated by retinoid X receptors

28 6,610,742 T Treatment of T-helper cell type 2-mediated immune diseases by retinoid antagonists

29 6,603,012 T RAR selective retinoid agonists

30 6,586,455 T Treatment of liposarcomas using a combination of thiazolidinediones and retinoid X receptor selective agonists

31 6,583,184 T Compositions having comfrey and methods for reducing retinoid-induced skin irritation

32 6,555,690 T Alkyl or aryl substituted dihydronaphthalene derivatives having retinoid and/or retinoid antagonist-like biological activity

33 6,545,009 T Retinoid-related receptor function regulating agent

34 6,538,149 T ARYL OR HETEROARYL SUBSTITUTED 3,4-DIHYDROANTHRACENE AND ARYL OR HETEROARYL SUBSTITUTED BENZO [1,2-G]CHROM-3-ENE, BENZO[1,2-G]-THIOCHROM-3-ENE AND BENZO [1,2-G]-1,2-DIHYDROQUINOLINE DERIVATIVES HAVING RETINOID ANTAGONIST OR RETINOID INVERSE AGONIST TYPE BIOLOGICAL ACTIVITY

35 6,537,568 T Implant device with a retinoid for improved biocompatibility

36 6,528,677 T Selective retinoid agonists

37 6,521,624 T Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

38 6,479,670 T Selective retinoid acid receptor agonists

39 6,469,028 T Synthesis and use of retinoid compounds having negative hormone and/or anatgonist activities

40 6,465,663 T O- or S-substituted tetrahydronaphthalene derivatives having retinoid and/or retinoid antagonist-like biological activity

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48 6,403,638 T 2,4-pentadienoic acid derivatives having selective activity for retinoid X (RXR) receptors

49 6,388,105 T Benzofuran, indole or benzothiophene 2,4-pentadienoic acid derivatives having selective activity for retinoid X (RXR) receptors

50 6,387,950 T Treatment of tumors with RAR.alpha. selective retinoid compounds in combination with other anti-tumor agents

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REVIEW ARTICLE

Drugs 1997 Mar; 53 (3) 358-388
0012-6667/97/0003-0358/$31.00/0

Current Use and Future Potential Role of Retinoids in Dermatology

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EXHIBIT 2

Summary

Since their introduction 15 years ago, retinoids have been increasingly used for topical and systemic treatment of psoriasis and other hyperkeratotic and parakeratotic skin disorders, keratotic genodermatoses, severe acne and acne-related dermatoses, and also for therapy and/or chemoprevention of skin cancer and other neoplasia. Oxidative metabolites of vitamin A (retinol) are natural retinoids present at low levels in the peripheral blood. Synthetic retinoids are classified into 3 generations including nonaromatic, monoaromatic and polyaromatic compounds. They are detectable in plasma 30-60 minutes after systemic administration, and reach maximum concentrations 2 to 4 hours later. Elimination half-life is 10 to 20 hours for isotretinoin, 80 to 175 days for etretinate and 2 to 4 days for *trans*-acitretin; the latter, however, partially converts into etretinate. Retinoid concentrations in skin are rather low in contrast to subcutaneous fat tissue.

Intracellularly, retinoids interact with cytosolic proteins and specific nuclear receptors. Two classes of nuclear receptors have been suggested to mediate retinoid activity at the molecular level, RARs and RXRs. The expression of retinoid receptors is tissue specific; skin mainly espresses RARγ and RXRα. Retinoids affect epidermal cell growth and differentiation as well as sebaceous gland activity and exhibit immunomodulatory and anti-inflammatory properties.

Current retinoid research targets the development of receptor-selective retinoids for tailoring and/or improving their therapeutic profile. Currently, tretinoin is used systemically for acute promyelocytic leukaemia, etretinate and acitretin for psoriasis and related disorders, as well as other disorders of keratinisation, and isotretinoin for seborrhoea, severe acne, rosacea and acneiform dermatoses. Systemic retinoids are also applied for chemoprevention of epithelial skin cancer and cutaneous T cell lymphoma. The major adverse effect of retinoids is teratogenicity; all other adverse effects are dose-dependent and controllable. Contraception is, therefore, essential during retinoid treatment in women of child-bearing age. Clinical monitoring requires physical examination for adverse effects every 3 to 4 weeks and proper laboratory investigations, also including analysis of retinoid bioavailability in selected cases. Topical retinoids are rapidly developing at present and seem promising for the future; their clinical application includes acne, aging, photodamage, precanceroses, skin cancer and disorders of skin pigmentation. The development of receptor-specific retinoids for topical treatment of psoriasis and/or acne may lead to interesting new compounds based on our current concepts of retinoid function.

'Retinoids' is a generic term that includes both naturally occurring molecules and also synthetic compounds showing specific biological activities resembling those of vitamin A (retinol). Such compounds can exhibit their specific biological activity without being vitamin A analogues chemically, i.e. without showing 'four isoprenoid units joined in a head-to-tail manner,' as defined by the IUPAC-IUB (International Union of Pure and Applied Chemistry-International Union of Biochemistry) Joint Commission on Biochemical Nomenclature.[1] Also, not all biologically active synthetic retinoids are carried by cytosolic binding proteins such as cellular retinol binding proteins (CRBP) or cytosolic retinoid acid binding proteins (CRABP), and binding to or activation of nuclear retinoid receptors may not be a necessary precondition for their action.

A series of natural and synthetic retinoids influence epithelial cell proliferation and epidermal dif-

ferentiation, and a few selected compounds also exert sebosuppressive effects. Based on these major properties, the group of retinoids were introduced in 1977/78 into dermatology[2] and broad spectrum dermatological therapy was envisaged for the 1980s.[3,4]

During the past decade, retinoids have been increasingly used (a) for treatment of hyperkeratotic and parakeratotic skin diseases, with or without dermal inflammation, and for a series of keratotic genodermatoses; (b) as a standard modality for treating severe acne and acne-related dermatoses; and (c) for treatment and/or chemoprevention of skin cancer and other neoplasia because of their immunomodulating activities, and their properties to promote differentiation and induce apoptosis, not only in epithelial tissues. The role of retinoids in oncology may potentially increase in the future.[5]

Table I. Some synthetic first and second generation retinoids

Retinoid	Remarks
First generation: nonaromatic retinoids	
Retinyl palmitate	Included in cosmetic preparations
Retinyl aldehyde	Included in cosmetic preparations
Tretinoin (all-*trans*-retinoic acid)	Most-studied retinoid: active systemically in acute myeloid leukaemia
Isotretinoin (13-*cis*-retinoic acid)	Sebosuppression, anti-inflammatory action; best agent for acne
9-*cis*-Retinoic acid	RXR-ligand; less active retinoid
α-14-Hydroxy-retro-retinol	Sustains B cell growth and T cell activation
Fenretinide [*N*-(4-Hydroxyphenyl)-retinamide]	Studied in chemoprevention trials
E 5166 (polyprenoic acid)	Studied in chemoprevention trials
Second generation: monoaromatic retinoids	
Etretinate	Psoriasis, disorders of keratinization
Acitretin	Psoriasis, disorders of keratinization
Isoacitretin (13-*cis*-acitretin)	Inactive (?) acitretin metabolite
Motretinide	Mild topical agent

Abbreviation: RXR = retinoid X receptor.

1. Vitamin A (Retinol), Natural Retinoids and the Skin

Vitamin A and its 2 metabolic derivatives, retinaldehyde and retinoic acid, are fat-soluble unsaturated isoprenoids necessary for growth, differentiation and maintenance of epithelial tissues, and also for reproduction. In a reversible process, vitamin A is oxidised *in vivo* to give retinaldehyde, which is important for vision. The normal plasma level of vitamin A in humans is 0.35 to 0.75 mg/L.[6]

Retinoic acid is a major oxidative metabolite of vitamin A, and can substitute for vitamin A in vitamin A–deficient animals in growth promotion and epithelial differentiation. However, it cannot be a substitute in completely maintaining reproduction. The stereoisomers all-*trans*-retinoic acid and 13-*cis*-retinoic acid are normal constituents of human serum.[7] Unlike the vitamin A esters which are stored in the liver, retinoic acid is not stored but is rapidly excreted. The normal levels in human plasma are 0.55 to 1.20 μg/L for all-*trans*-retinoic acid and 0.80 to 2.40 μg/L for 13-*cis*-retinoic acid.[8]

Endogenous retinoids are unlikely to be involved in the pathogenesis of common skin diseases, such as acne and psoriasis.[6,8] In contrast, hypervitaminosis A is associated with a broad spectrum of symptoms resembling the mucocutaneous adverse effects of oral treatment with synthetic retinoids. In humans, 0.8 to 1 mg or 2400 to 3000 IU of vitamin A is required per day (1 IU = 0.3mg). However, vitamin A intoxication may occur when daily dietary intake of vitamin A exceeds 18 000 to 60 000 IU/day in children and 50 000 to 100 000 IU/day in adults, given over a period of several months.[9] With restricted liver metabolic capacity, symptoms of intoxication may appear much earlier, within a few months and when smaller doses are taken (10 000 IU/day).

Hypervitaminosis A is signaled by an increase in vitamin A ester levels (normal value is 5 to 8% of vitamin A value) in serum. The vitamin A values rarely increase. Pregnant women and women of childbearing age should not exceed an oral vitamin A intake of 8000 to 10 000 IU/day.

2. Synthetic Retinoids

2.1 Active Groups and Classification

In the search for more biologically active and less toxic compounds, all 3 portions of the vitamin A molecule have been chemically modified.[10] Three generations – nonaromatic, monoaromatic and polyaromatic retinoids – are known today[11,12] (see tables I and II).

It was found early on that alterations of the polyene chain may diminish retinoid activity. Modifications and/or esterification of the carboxylic end group are often associated with reduced toxicity while biologic activity is maintained or even enhanced. Substitutions for the ring were found to yield less toxicity with a marked increase of the biological activity of the molecule. In further developmental work, additional aromatic rings were introduced; some new retinoids barely resemble the original vitamin A molecule, such as the naphthalenecarboxylic acids derivatives,[10] adapalene[13,14] (see Adis Drug Evaluation later in this issue[262]) or tazarotene.[15]

The discovery of nuclear retinoid receptor protein families and the identification of tissue/cell specificities have led to new concepts such as receptor-selective retinoids; agonists, neutral antagonists and inverse agonists,[16] with the aim of targeting their action, thus improving the overall therapeutic profile. However, the existence of retinoids which are biologically active without binding to retinoid transport proteins and to specific nuclear receptors may interfere with this concept.

Table II. Arotinoids (third generation retinoids) introduced into phase 1 studies and partly in clinical use

Temarotene (Ro 15-0778; nonpolar parent compound)	Apparently inactive
Arotinoid acid (Ro 13-7410)	Activity profile still unknown
Arotinoid ethyl ester (Ro 13-6298)	Potent antipsoriatic agent; also active in keratinising disorders and cutaneous T cell lymphoma?
Arotinoid ethyl sulphone (Ro 15-1570)	Antipsoriatic properties
Arotinoid methyl sulphone (Ro 14-9706)	Activity profile still unknown
Adapalene (CD 271)	Antiacne agent (topical)
Tazarotene (AGN 190168)	Antipsoriatic agent (topical)

2.2 Synthetic Retinoids in Current Use

All-*trans* retinoic acid (tretinoin) was the first retinoid to be synthesised. Although this compound is now established for topical therapy, its systemic use did not reveal significant advantages over vitamin A. However, recently the drug showed beneficial effects in acute promyelocytic leukaemia.

13-*cis*-Retinoic acid (isotretinoin) is an extremely effective drug if given systemically in severe forms of acne. It has marked sebostatic activity after oral intake but its topical use strongly diminishes or cancels out sebosuppression. Compared with topical tretinoin, topical isotretinoin and also retinaldehyde exhibit almost identical biological activities, with the exception of a less pronounced irritative effect;[17,18] in addition, vitamin A palmitate is used as an ingredient in cosmetic preparations.

When the first monoaromatic compound, etretinate, was developed, a real breakthrough in the treatment of severe psoriasis and other dermatoses was achieved. The better ratio between therapeutic efficacy and adverse effects resulted in its widespread clinical use. Its free acid metabolite, acitretin, was later found to be similarly effective, with a much shorter elimination half-life ($t_{1/\beta}$) that was advantageous for therapeutic use. The fact that re-esterification *in vivo* may convert acitretin into etretinate, however, cancelled out its major advantage when compared to its precursor. Motretinide, an ethylamide of the aromatic compound, is also available in Europe for topical treatment.

Polyaromatic retinoids, also called arotinoids, represent the third synthetic retinoid generation. These compounds have been in animal and clinical research for 15 years, but it was only recently that two of them were almost simultaneously introduced for topical treatment of acne (adapalene)[19]

Table III. Pharmacokinetic properties of etretinate, *trans*-acitretin and isotretinoin

Parameter	Etretinate	*trans*-Acitretin	Isotretinoin
Bioavailability	40% (range 30-70%)	20-90%	25%
C_{max}	237-1403 µg/L Dose 50-70mg	196-728 µg/L Dose 50mg	366 ± 159 µg/L Dose 80mg
t_{max}	2-3h	1-4h	3h (1-4h)
Elimination half-life	80-175 days	2-4 days	10-20h
Metabolites	*trans*-acitretin, 13-*cis*-acitretin	13-*cis*-acitretin, etretinate	4-oxo-isotretinoin

Abbreviations: C_{max} = maximum plasma concentration; t_{max} = time to C_{max}.

and psoriasis (tazarotene).[15] There is increasing evidence that others will follow.

3. Pharmacokinetic Properties and Clinical Relevance

Oral retinoids have been administered for the treatment of skin disease for more than 25 years,[20] and established preparations are available for dermatological use today. Because of their teratogenic properties, however, considerable concern has been raised during the past decade, requiring a better understanding of their pharmacokinetics (table III) and the relevance of circulating retinoid blood concentrations.[21-24]

3.1 Absorption and Distribution

The bioavailability of oral isotretinoin is approximately 25%, and can be increased by food 1.5- to 2-fold. After 30 minutes the drug is detectable in the blood, and maximum concentrations are reached 1 to 4 hours after oral intake. In some cases, secondary and tertiary concentration maxima consistent with an enterohepatic circulation may occur.

The main metabolite, 4-oxo-isotretinoin (fig. 1) is present in plasma in a 2- to 4- fold higher concentration 6 hours after a single dose, and steady-state concentrations are reached after 1 week. The $t_{1/2\beta}$ of isotretinoin ranges from 10 to 20 hours while that of its metabolites ranges from 11 to 50 hours. Isotretinoin crosses the placenta.[25,26]

The aromatic retinoid ethylester etretinate is readily hydrolysed after oral intake to its free carboxylic acid, acitretin, in a *cis-trans*-isomeric form. Its bioavailability is about 40%, with large interindividual variations, since retinoid absorption from the gut is enhanced by fat-rich food. In plasma, most synthetic retinoids are bound to lipoproteins; only less than 2% of etretinate circulates as free drug.

One hour after oral administration, etretinate, *trans*-acitretin and 13-*cis*-acitretin (fig. 2) can be detected in plasma, reaching maximal levels in 2 to 4 hours. Remaining amounts of the parent ester compound are stored in the subcutaneous fat compartment, with slow elimination characteristics and a $t_{1/2\beta}$ of 80 to 175 days after multiple doses. The plasma concentrations during a long term washout period (more than 2 years) are extremely low, being most likely therapeutically ineffective, but potentially teratogenic.[27] Interestingly, overweight patients tend to have slower elimination rates, maintain higher serum concentrations, and clear etretinate later.[28]

From the clinical point of view, teratogenicity is the major issue in retinoid treatment because nearly all known retinoid compounds will be transferred through the placenta and be secreted in breast milk, as shown in animal studies.[26,29,30]

Trans-acitretin has a much shorter $t_{1/2\beta}$ than etretinate – about 2 to 4 days following cessation of

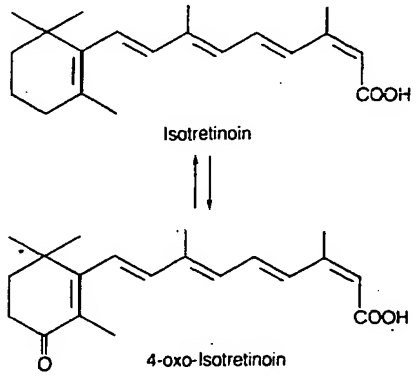

Fig. 1. Isotretinoin and its metabolite 4-oxo-isotretinoin.

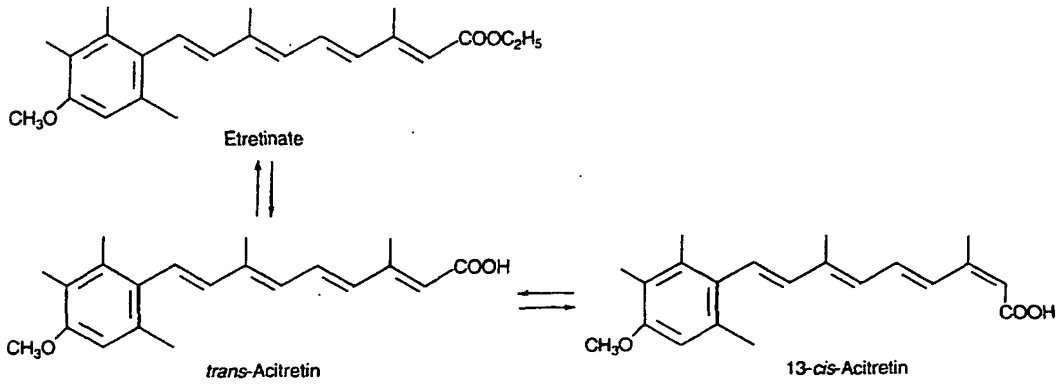

Fig. 2. Etretinate and its metabolites *trans*-acitretin and 13-*cis*-acitretin.

treatment. Similar to other retinoids, *trans*-acitretin is incompletely absorbed, with its oral bioavailability ranging from 20 to 90%. Absorption increases when the drug is administered with food,[31] and more than 99% of the absorbed drug binds to plasma proteins.[32]

Trans-acitretin and its metabolite 13-*cis*-acitretin are interconverted, and the individual role of the 2 metabolites in the overall therapeutic effect has not been fully clarified. Steady-state plasma concentrations of *trans*-acitretin are reached within 1 to 2 weeks. One month after cessation of a 2- to 7-month treatment period, the residual plasma concentrations of *trans*- and *cis*-acitretin remain below the detection limit, and the risk for teratogenicity appears minimised.[33]

3.2 Metabolism and Elimination

The major metabolites of isotretinoin in blood are 4-hydroxy- and 4-oxo-isotretinoin, while several glucuronide conjugates are detectable in the bile.[34] Since there is interconversion between the 2 isomers isotretinoin and tretinoin *in vivo*, about 10 to 30% of the drug is metabolised via tretinoin. Excretion of isotretinoin occurs after conjugation with the faeces or after metabolism with the urine. The potential clinical activity of the isotretinoin metabolites, including the glucuronides, is under ongoing research.

The metabolism of etretinate includes its hydrolysis to *trans*-acitretin, isomerisation to 13-*cis*-acitretin, oxidation to more water-soluble compounds, and conjugation to glucuronides, followed by biliary excretion: only a small part is excreted via the urine. Pharmacological studies indicate that etretinate may be acting as a prodrug for *trans*-acitretin, but when esterase is added to an *in vitro* system the 2 compounds are equipotent.

While etretinate has a $t_{1/\beta}$ of 100 days, *trans*-acitretin has a $t_{1/\beta}$ of only 2 to 4 days.[32] The latter is metabolised into at least 4 compounds,[35] one of which is 13-*cis*-acitretin.[36,37] Because of their polar carboxylic acid group, *trans*- and 13-*cis*-acitretin are less likely than etretinate to accumulate in subcutaneous tissue. Both are widely distributed and are excreted in faeces and urine.

Administration of *trans*-acitretin instead of etretinate was therefore considered as a preferable therapeutic option in psoriasis,[38-40] based on the assumption that a shorter period of contraception would be advantageous for women. However, partial *in vivo* conversion of *trans*-acitretin into etretinate has been described *in vivo*, and etretinate at concentrations of 5 to 100 µg/L was recently detected in patients treated with oral *trans*-acitretin.[41,42] Re-esterification does take place under varying conditions in healthy volunteers and patients with psoriasis, as well in animal models and *in vitro*.[43] Alcohol appears to be an important

contributing factor for the formation of etretinate, but oral intake of alcohol is not a necessary precondition for re-esterification.[44,45]

3.3 Epidermal Transport and Metabolism

Epidermal concentrations of isotretinoin are rather low,[46] and no progressive accumulation in serum, epidermis or the subcutis has been found. After discontinuation of therapy, isotretinoin disappears from serum and skin within 2 to 4 weeks. It seems likely that isotretinoin therapy interferes with the endogenous metabolism of vitamin A in the skin because vitamin A levels increased by about 50% and dihydrovitamin A levels decreased by around 80% in some patients.[46]

Etretinate appears in human epidermis shortly after oral administration. Therapeutic levels are reached within 7 to 10 days, with no evidence of accumulation even after further oral intake. The concentrations are similar in lesional and in non-lesional skin, and also in plasma of patients with psoriasis.

The amount of etretinate and *trans*-acitretin[47] has little effect on endogenous vitamin A metabolism in skin. When treatment is discontinued, epidermal etretinate decreases rapidly, and mucocutaneous adverse effects associated with high blood drug concentrations disappear in a few days. The drug, however, accumulates in the subcutaneous fat tissue, reaching levels 20 to 30 times higher than those in the epidermis.[30]

The tissue distribution of etretinate is widespread, including the adrenals and several other organs in low concentrations. Interestingly, adipose tissue contains almost exclusively etretinate, whereas in the liver *trans*-acitretin predominates. *trans*-Acitretin concentrations in subcutaneous fat varied from 15 to 1437 μg/L.[47,48] Relatively low concentrations of both drugs were detected in suction blister fluid at steady-state, indicating that only minor proportions are free to diffuse outside the vascular space.[42]

4. Mechanisms of Action

Although vitamin A is assumed to enter the cells by non–receptor-mediated endocytosis, the exact mechanisms of retinoid-induced phenomena, including membrane-associated signal transduction, need to be elucidated.[49,50] Intracellularly, retinoids interact with cytosolic proteins[49,50,52] and nuclear receptors.[49,51,53,54] They induce expression of genes which bear specific DNA sequences recognising the retinoid/receptor complex. These pathways have been well investigated for all-*trans* retinoic acid but they may not be valid for all retinoids.

4.1 Retinoid Receptors and Gene Regulation

Two classes of nuclear retinoid receptors were suggested to mediate retinoid activity at the molecular level [retinoic acid receptors (RARs) and retinoid X receptors (RXRs)], members of the steroid-thyroid hormone superfamily. They act as ligand-dependent transcriptional factors. RARs can bind both all-*trans* and 9-*cis*-retinoic acid with high affinity, while RXRs selectively interact with 9-*cis*-retinoic acid. In contrast, 13-*cis*-retinoic acid shows low affinity for RARs. 14-Hydroxy-retroretinol, which specifically induces lymphocyte proliferation, does not bind to or activate retinoid receptors,[55] acitretin does not bind to but activates RARs, and Ro 40-1349 binds to but does not activate RARs.[53] These controversial data indicate the existence of other, unknown signalling pathways for retinoid action (table IV).

Recently, RARα, RARβ and RARγ have been identified as being encoded by distinct genes mapped on respective chromosomes 17q21.1, 3p24 and 12q13.[56-58] Each RAR gene generates multiple isoforms. The human RXR family also includes 3 members, RXRα, RXRβ and RXRγ; their genes are mapped on chromosomes 9q34.3, 6p21.3 and 1q22-23, respectively.[59,60]

The expression of RARs is tissue-specific. Abundant expression of RARγ and RXRα, low

Table IV. Nuclear and cytosolic receptor binding of synthetic retinoids

Compound	Binding affinity EC_{50} (see key below)		
	RARs	RXRs	CRABP
Agonists			
all-*trans*-Retinoic acid	1(α = β = γ)	4	1
9-*cis*-Retinoic aicd	1(α = β = γ)	2	3
4-Oxo-retinoic acid	3		
4-Hydroxy-retinoic acid	4		
E-5166 (polyprenoic acid)	2		2
Arotinoic acid	1		2
CD-367	1		1
TTNPB	2(β = γ > α)		
LGD-1069 (retinoid oxime)	4	2	
LG-100268	4	2	
Selective agonists			
Am580 (Ro40-6055)	2(α), 4(β,γ)	3	
Adapalene	2(β), 3(γ), 4(α)	–	
Tazarotenic acid	2(β), 3(γ), 4(α)	–	
TTNN (Ro 19-0645)	2(β), 3(α)		
CD-437 (AHPN)	2(γ), 4(β > α)		
CD-2325	2(γ), 4(α = β)		
Ro 26-4453	–	2(α)	
AGN-191701	–	RXRs	
SR-11217	–	RXRs	
SR-11237	–	RXRs	
Antagonists			
Ro 41-5253	RARα		
AGN-193109	1 (α = β = γ)		
Active compounds without affinity for receptors			
Vitamin A (retinol)	4		3
13-*cis*-Retinoic acid	3[a]	–	–
α-14-Hydroxy-retro retinol	–	–	–
Etretinate	–	–	–
Acitretin	–	–	3
Arotinoid ethyl ester			–
Arotinoid ethyl sulphone			–
CD-2398	–		
Anti AP-1–selective compounds			
SR-11327	RARα > RARβ > RARγ	RXR < RARγ	
SR-11238	RARβ > RARγ > RARα	RXR < RARγ RXR ≥ RARα	

a controversial results, moderate or no binding reported.

Abbreviations and symbols: CRABP = cellular retinoic acid binding protein; EC_{50} = concentration binding 50% of the receptors; RAR = retinoic acid receptor; RXR = retinoid X receptor; 1 = ≤10 nmol/L; 2 = ≤100 nmol/L; 3 = ≤1000 nmol/L; 4 = ≤10000 nmol/L; – = inactive.

amounts of RARα and no RARβ were shown in normal and psoriatic human epidermis.[51,61]

Retinoid receptors regulate the transcription of genes bearing short DNA sequences in their promoter regions, known as retinoid-responsive elements (RAREs and RXREs). They are bound by receptor heterodimers (RXR/RAR) or homodimers (RXR/RXR) with higher affinity than for individual receptors.[62] All-*trans* retinoic acid has been shown to induce several genes bearing retinoid-responsive elements.

Three retinoid receptor/target gene interactions are of particular interest. First, a positive feedback mechanism: all 3 RAR genes contain a retinoid-responsive element and the autoinduction of RAR expression in some tissues could lead to a potential amplification of retinoid effects.[55] Secondly, a negative feedback mechanism: retinoic acid–induced overexpression of CRABP-I in F9 mouse teratocarcinoma cells led to reduction of a certain subset of retinoic acid–responsive genes. Possibly, retinoid-binding proteins may antagonise retinoid interaction with nuclear receptors.[63] Thirdly, interaction with other signal transduction mechanisms: interaction with transcription factors activated by other signal transduction mechanisms, e.g. AP-1,[64] may produce specific retinoid effects. Retinoids with selective inhibition of AP-1 were shown to reduce F9 teratocarcinoma cell growth without influencing cell differentiation.[65]

These interactions become more complicated since in addition to RAR agonists, RAR neutral antagonists and RAR inverse agonists have been synthesised.[16] Inverse agonists bind to RARs and repress their basal transcriptional activity. Neutral antagonists do not change the basal activity of RARs but can inhibit the transcriptional activation effects of agonists as well as the transcriptional repression effects of inverse agonists.

4.2 Effects on Epidermal Cell Growth and Differentiation

Retinoids act as modulators of epidermal growth and supervisors of differentiation. They promote cell proliferation in normal epidermis,

both topically and systemically, but act towards normalisation in hyperproliferative epithelia. Psoriatic keratinocytes are down-regulated by retinoids. *In vitro*, retinoic acid has been shown to either stimulate or inhibit epidermal keratinocyte proliferation, depending on the growth-culture conditions.

Possibly, retinoids induce and modulate the expression of growth factors and their receptors. Stimulation of keratinocyte proliferation is associated with induction of cyclic adenosine monophosphate (cAMP), epidermal growth factor (EGF) receptor binding, protein kinase C (PKC) and transforming growth factor (TGF)-α, while TGF-β_2–regulated inhibition of EGF binding to its receptor leads to down-regulation of cell growth.[66,67] The effect of retinoic acid on EGF receptor binding is on a region of the EGF promoter, regulated by RARγ.

Parallel to these effects, retinoids are known to alter terminal differentiation towards a nonkeratinising, metaplastic, mucosa-like epithelium.[68] The glycosylation pattern of normal skin treated with retinoic acid resembles that of a mucosal epithelium,[69] with a reduction of tonofilaments, decreased corneocyte cohesiveness, impaired function of the permeability barrier, and increased transepidermal water loss, thus explaining the keratolytic effect of retinoids in hyperkeratotic disorders. In contrast, oral and topical retinoids stimulate and maintain terminal differentiation of human epidermal cells, e.g. in the psoriatic plaque.

In vitro, most markers of terminal differentiation (loricrin, transglutaminase, involucrin, filaggrin, keratins 1 and 10) are down-regulated by retinoic acid in a dose-dependent manner. Keratins 19 and 13, markers of nonstratified and wet stratified epithelia, respectively, are induced by retinoic acid.[68,70] In contrast, natural retinoic acid concentrations (10^{-9} to 10^{-8} mol/L) restored the architecture of the 'epidermis' in the air-medium interface model, which exhibited excessive hyperkeratosis in vitamin A–depleted medium.[71] Adapalene induced similar effects in this model, despite its different receptor affinity and its inability to bind to CRABP.[72]

The involvement of retinoid receptors in the modulation of proliferation and differentiation of malignant epithelial tissue was investigated on T47D breast carcinoma ER+ cells *in vitro* (W. Bollag, personal communication). RARα-selective agonists, but not RARβ, RARγ and RXRα agonists, inhibited T47D cell growth and induced differentiation. Addition of an RARα antagonist neutralised the RARα agonist effects. In contrast, all retinoids induced apoptosis of MCF7 breast carcinoma ER+ cells *in vitro*.

4.3 Effects on Sebaceous Gland Activity and Epidermal Lipids

Isotretinoin is the most effective drug in reducing sebaceous gland size (up to 90%) by decreasing proliferation of basal sebocytes and suppressing sebum production *in vivo*. Marked decrease of wax esters, a small decrease of squalene and a relative increase in cholesterol level have been detected in skin surface lipids. Oral isotretinoin has also been shown to decrease triglyceride fraction, whereas free sterols and total ceramides were increased in comedonal lipids.[13] All-*trans*-retinoic acid and 9-*cis*-retinoic acid were recently found to be less effective than isotretinoin in sebum suppression.[73,74]

Current *in vitro* studies have confirmed the pronounced, direct inhibitory effects of isotretinoin on proliferation and lipid synthesis of human sebocytes *in vitro*,[75-77] controlling their differentiation and antigen expression.[78] The molecular basis for this antisebotrophic activity has not been elucidated, but the cyclohexenyl ring may be necessary for pronounced sebum suppression. Since isotretinoin has low affinity for nuclear retinoid receptors and retinoic acid–binding proteins, it is likely that sebosuppression is not a directly receptor-mediated retinoid effect. Arotinoids may enhance the antikeratinising activity when bearing a carboxylic acid end group but abolish the sebosuppressive activity in humans.

4.4 Immunomodulatory and Anti-Inflammatory Properties

There is some early information concerning the activity of retinoids on immunomodulatory dermal processes.[79-84] In a more recent *in vitro* study, isotretinoin, etretinate and acitretin were shown to inhibit the proliferation of dermal microvascular endothelial cells, without influencing the expression of human leucocyte antigen (HLA)-DR and intercellular adhesion molecule (ICAM)-1.[85]

The inhibition of angiogenesis was further investigated in T47D cell–induced tumours (W. Bollag, personal communication). All retinoids tested inhibited angiogenesis, independent of their receptor selectivity, but addition of an RARα antagonist neutralised the angiosuppressive retinoid effect.

Retinoids are generally thought to stimulate humoral and cellular immunity, although immune-inhibitory effects have been also described. 14-Hydroxy-retro-retinol, a natural retinoid, was identified to be an essential growth factor for lymphoblastoid cells.[86] Retinoids can enhance antibody production, increasing peripheral blood T helper cells but not natural killer cells. Topically applied tretinoin was shown to prevent Langerhans cell depletion from human epidermis due to UV light,[87] suggesting that normalisation of Langerhans cell distribution in psoriatic skin during systemic etretinate treatment may be a direct retinoid effect.

Cell surface antigens of T cells and natural killer cells have been reported to increase after retinoid exposure *in vitro*.[88] Interaction of retinoids and cytokines has been suggested, because of the stronger differentiation response of HL-60 cells to combined tretinoin and cytokines, especially interferon (IFN)-γ.[89] At the molecular level, the modulation of RARα gene expression in chicken T lymphocytes by vitamin A and tretinoin indicates that antigen-specific proliferative responses of T lymphocytes may be directly influenced by tretinoin via modulation of RARα expression.[90]

Retinoids exhibit anti-inflammatory activity. The loss of neutrophil migration from dermal capillaries to the epidermis in psoriatic skin with oral etretinate/acitretin or topical retinoid therapy is well documented.[80,81] In addition, topical isotretinoin was found to be more potent in inhibiting leukotriene B_4–induced migration of polymorphonuclear cells into human skin than tretinoin and arotinoids.[91] Isotretinoin and tretinoin inhibited nitride oxide and tumour necrosis factor (TNF)-α production by human keratinocytes, and reduced inducible nitride oxide synthase mRNA levels.[82]

Table V. Topical and systemic retinoids in clinical use

Retinoid	Concentration/vehicle	Indications
Topical		
Retinyl palmitate	0.5-5% emulsions	Cosmetic agents
Retinyl aldehyde	0.05% cream	Cosmetic agents
Tretinoin	0.025%-0.1% creams, 0.05-0.1% solutions, 0.025-0.05% gels	Mild forms of acne, photodamaged skin, skin aging
Isotretinoin	0.05% gel	Mild forms of acne
Motretinide	0.1% cream, 0.1% solution	Mild forms of acne
Adapalene	0.1% gel	Mild form of acne
Tazarotene	0.05-0.1% gels	Psoriasis
Systemic		
Tretinoin		Acute promyelocytic leukaemia
Isotretinoin		Severe acne and acne-related dermatoses
Etretinate		Psoriasis, genokeratoses
Acitretin		Psoriasis, genekeratoses

5. Therapeutic Use

The clinical use of several retinoids is now well established[92-94] (see table V).

5.1 Psoriasis and Related Disorders

Several attempts have been made in the past to treat psoriasis systemically, including the use of arsenic, corticosteroids, methotrexate, psoralens, cyclosporin and other cytotoxic drugs. The topical and also the oral application of retinoic acid and

the first synthetic derivatives was reported by our group as early as 1972.[95-97]

Today, oral retinoids represent the mainstream of systemic antipsoriatic treatment, particularly in severe pustular and erythrodermic types. Etretinate/acitretin are superior to isotretinoin in their antipsoriatic action. They are administered alone or in combination with other modalities (mild corticosteroids, dithranol, tar) and/or with phototherapies (UVB or PUVA).[93,98-100]

In plaque-type psoriasis the lesions slowly enlarge, flatten and gradually disappear with oral etretinate/acitretin therapy. The drugs seem appropriate both for initial treatment and for maintenance in low dosage. In pustular types (type Zumbusch, psoriasis inversa, acrolocalised suppurative pustulosis Hallopeau) it was recognised early that oral etretinate/acitretin is the treatment of first choice,[101] including palmoplantar pustulosis[102] as a variant.

In pityriasis rubra pilaris,[103] clinical experience has been somewhat contradictory, but overall there is a beneficial effect, particularly in juvenile types of the disease. In a recent review, the early use of oral retinoids in this variant was seen as offering the best available chance for clearing.[104]

5.1.1 Antipsoriatic action

The antipsoriatic action of retinoids is not fully understood. Their cutaneous effects are rather nonspecific and, therefore, a large spectrum of disorders of keratinisation respond. It seems that the monoaromatic retinoids of the second generation:

- reduce the proliferation rate in acanthotic epidermis by downregulating the number of cycling cells;
- promote terminal differentiation and filaggrin synthesis in malpighian keratinocytes;
- regulate desquamation of the corneocytes restoring normal transglutaminase activity levels.

Their dermal effects consist of modulation of lymphocyte functions and inhibition of neutrophilic migration. Psoriatic inflammation gradually ceases after long term oral treatment over 6 to 12 weeks. It is now well accepted that retinoids work slowly but reliably in psoriasis if the dosage is correct and the patients remain under careful supervision.

5.1.2 Dosage and Interactions

The dosage required for antipsoriatic treatment is 0.3 to 1.0 mg/kg/day etretinate or acitretin, administered in 1 or 2 daily doses with meals.[105] The gold standard remains 0.5 to 0.6 mg/kg/day given over a period of 6 to 12 weeks. Drug absorption is increased 2- to 5-fold, and is more consistent, if taken with fatty foods. The initial dose level may vary individually according to the needs of the patient, type of the disease, previous treatments and concomitant drug intake.

Retinoid monotherapy is preferred and is always recommended by us, because of various interactions of retinoids, e.g. with ketoconazole, phenytoin, carbamazepine, barbiturates, tetracyclines, aspirin and most likely also with other nonsteroidal anti-inflammatory drugs. No interaction of acitretin with phenprocoumon has been found.[106] Also, retinoids do not interfere with oral contraceptive efficacy.[107]

A major advantage of retinoids in psoriasis and disorders of keratinisation is that they act synergistically with other common treatments, such as topical corticosteroids, dithranol, tar and also UVA/UVB phototherapies. In combined schedules the oral dosage of etretinate or acitretin can be reduced to 0.3 to 0.5 mg/kg/day, thus minimising their adverse effects. The RePUVA (retinoid + PUVA) technique is considered today as a most effective treatment modality for recalcitrant severe psoriasis;[108,109] over 80 to 90% of all cases can be cleared after 20 to 30 UV sessions and response can be maintained on low-dose oral retinoid treatment. The rate of relapse after withdrawal of therapy, however, is 20 to 50% during the first 6 months, comparable to dithranol and UVB treatments. Also, the combinations of topical dithranol and selective UV phototherapy (ReSUP) have been recognised, and are well accepted for treatment of widespread psoriasis (table VI).

5.1.3 Etretinate/Acitretin

In randomised studies comparing the antipsoriatic potential of etretinate with acitretin, only

slight differences concerning efficacy (30 to 50% complete remission of moderate to severe plaque-type psoriasis within 4 to 8 weeks; 71 to 83% marked or complete remission after 12 weeks) and relapse rates (46.7% *vs* 40.6%, respectively) were registered.[38,39,111] Etretinate concentrations may persist in plasma after changing therapy to acitretin.[112] However, the adverse effect profile of acitretin appeared more pronounced at dosage levels exceeding 35 to 40 mg/kg/day. Mucocutaneous adverse effects such as xerosis, palmoplantar desquamation and hair loss were seen at higher rates with acitretin. Thus, most investigators limit the dosage of acitretin to ≤40 mg/day: in lamellar ichthyosis ≤25 mg/day acitretin was found preferable.[113] We usually recommend administration of acitretin in 2 daily doses to avoid maximal peaks of absorption and, therefore, increased toxicity.

Since carboxylic acids are not stored in subcutaneous tissue but are more rapidly metabolised, it was originally thought that acitretin would replace etretinate in clinical practice; however, the therapeutic/toxocological profile of etretinate is less pronounced (e.g. adverse effects appear more slowly) and re-esterification does take place *in vivo*, with or without presence of alcohol.[44,114,115] Both drugs are now in clinical use, and long term contraception over 2 years after drug withdrawal for women of child bearing age is required for both (see section 6.6).

Table VI. Established treatment of psoriasis with etretinate/acitretin alone or in combination with other modalities. Other combinations of oral etretinate/acitretin with methotrexate, cyclosporin, hydroxycarbamide (hydroxyurea)[110] etc. do not seem recommendable, even if they work, because of increased toxicity

Plaque-type psoriasis
Monotherapy (or with topical dithranol): 0.3-1.0 mg/kg/day for 4-12wk
Combination with UVB (ReUVB, ReSUP): 0.3-0.5 mg/kg/day for 6wk
Combination with psoralen and UVA (PUVA) [RePUVA]: 0.3-0.5 mg/kg/day for 4-6wk
Erythrodermic psoriasis
Low initial dosage, slowly increasing up to 0.5-0.6 mg/kg/day over 3mo. Maintenance then required for 6mo
Pustular psoriasis
High initial dosage, slowly decreasing to 0.5-0.6 mg/kg/day over 3-6mo. Maintenance then required for 6-12mo

5.2 Other Disorders of Keratinisation

Oral retinoids of the first and second generation including isotretinoin, etretinate and acitretin are effective in several disorders of keratinisation,[93,116-119] since their action in promoting keratinocytic differentiation is not specific for psoriasis.

Oral retinoids have been shown to normalise hyperkeratotic and dyskeratotic conditions, and to reduce scaling in severe keratotic genodermatoses. Clearing is not complete, but the overall improvement of skin appearance and function justifies their use. Darier's disease,[120] ichthyosis vulgaris, congenital ichthyosis (particularly the dry lamellar type), various types of palmoplantar keratodermas, and also erythrokeratodermia figurata variabilis (Mendes da Costa) respond well or very well to etretinate/acitretin and represent standard indications for initiating oral retinoid treatment.[116,117,121] Etretinate or acitretin can be used in these conditions, whichever is available.

Isotretinoin appears inferior to the aromatic compounds because its strong sebostatic action may dry out the skin and cause physical discomfort. In most cases, treatment with a low initial dosage (0.3 to 0.6 mg/kg/day) is preferred in these indications for avoiding mucocutaneous adverse effects such as retinoid dermatitis, intertriginous maceration, oozing and also increased bulla formation, e.g. in epidermolytic hyperkeratosis. Of course, in these disorders treatment with minimal doses is life-long, since the genetic disease itself remains intractable. Therefore, teratogenicity and bone toxicity of oral retinoids should be monitored and controlled carefully in the mostly younger patient group.

Other rare keratotic diseases, such as ichthyosis hystrix, hyperkeratotic verrucous naevi, keratosis lichenoides chronica etc., may respond to standard oral retinoid doses to some degree, producing a reduction of hyperkeratosis and skin smoothening. Because of the rarity of such entities, however,

overall experience is still restricted to a limited number of cases. Finally, in porokeratosis Mibelli of the classical type, inflammatory linear verrucous epidermal naevi (ILVEN), pachyonychia congenita, Netherton's syndrome and monilethrix, the retinoid effect appears to be unsatisfactory.

5.3 Seborrhoea, Acne and Acneiform Dermatoses

5.3.1 Seborrhoea

Systemic isotretinoin is today the regimen of choice in severe seborrhoea, since it reduces sebocyte lipid synthesis by 75% with daily doses as low as 0.1 mg/kg, and by 90% with 0.3 to 0.5 mg/kg after 4 weeks. No other known agent can influence sebum production to the same extent. In addition, the number of proliferating sebocytes and the size of sebaceous glands decreases by 90% of the pretreatment values. In a recent double-blind trial, 9-*cis*-retinoic acid [0.3 mg/kg/day (20 mg/day)] was inferior to isotretinoin at the same dosage in 26 healthy volunteers, who had a high sebum excretion rate, after 4 weeks (37% sebum decrease with 9-*cis*-retinoic acid *vs* 91% with isotretinoin).[173] In another trial involving 12 healthy volunteers, oral tretinoin [0.26 mg/kg/day (20 mg/day)] did not affect sebum excretion rates.[174]

Current *in vitro* studies have confirmed the pronounced, direct inhibitory effects of isotretinoin on proliferation, lipid synthesis, and differentiation of human sebocytes,[175-177] as well as on reduction of sebaceous gland volume.[122] Inhibition of sebocyte proliferation and lipid synthesis were found to be independent mechanisms of isotretinoin action. Other nonaromatic retinoids, like tretinoin and 4-hydroxy-tretinoin also inhibited cell proliferation and lipid synthesis but to a lesser extent than isotretinoin, while didehydroretinoic acid and 9-*cis*-retinoic acid were as active as isotretinoin in suppressing proliferation of human sebocytes *in vitro*.[34,76,77]

In contrast, the second and third generation aromatic retinoids did not significantly reduce sebum synthesis in several clinical studies. Etretinate (1 mg/kg/day for 8 weeks), acitretin (0.3 to 1 mg/kg/day for 6 weeks) and arotinoid ethylester (1 µg/kg/day for 6 weeks),[123] esarotene (100 mg/day for 6 weeks),[124] and temarotene (1 mg/day to 2 g/day) for 8 to 12 weeks)[125,126] did not reveal notable sebosuppressive activity. Arotinoic acid, a very potent inhibitor of sebocyte differentiation in animal models, was inferior to isotretinoin in a few patients tested.[127] These retinoids were not sebosuppressive when applied topically.

Patients who have received oral isotretinoin therapy for seborrhoea do not usually experience relapse for months or years. However, the duration of the antiseborrhoeic effect seems to be dose dependent. Taking good tolerance into account, a dosage of 0.1 to 0.3 mg/kg/day over 4 weeks is sufficient to produce a sebostatic effect for at least 8 weeks after discontinuation of treatment. In our experience, 5 to 10 mg/day may be sufficient as a maintenance sebosuppressive dosage over several years.

5.3.2 Acne

Systemic administration of isotretinoin, introduced in 1979, revolutionised the treatment of severe acne.[128] Isotretinoin is the only drug that directly suppresses abnormal desquamation of sebaceous follicle epithelium and sebum production. Subsequently, the growth of *Propionibacterium acnes* is greatly diminished.

Isotretinoin affects all 4 pathogenic factors for acne, whereas oral 9-*cis*-retinoic acid (0.3 to 1 mg/kg/day),[129] etretinate (1 mg/kg/day), acitretin (0.3 to 1 mg/kg/day) and arotinoid ethylester (1 µg/kg/day),[123] esarotene (100 mg/day),[124] and temarotene (1 mg/day to 2 g/day)[125] were practically inactive. The clinical course of isotretinoin therapy shows more rapid improvement of inflammatory lesions as compared with comedones. Pustules are cleared earlier than papules or nodules, and lesions localised on the face, upper arms and legs tend to clear more rapidly than trunk lesions.

Some authors favour isotretinoin 0.5 mg/kg/day;[123] others advocate a higher dosage of 1 mg/kg/day.[130] A 6-month treatment course is sufficient for 99% of patients, but it has been documented that an initial dosage of 1 mg/kg/day for 3

months, then reduced to 0.5 and, if possible, to 0.2 mg/kg/day for 9 additional months will optimise the therapeutic outcome. Relapses may occur after a single 6-month course. A 22 to 30% relapse rate was noted in in patients followed for 10 years after isotretinoin 1 mg/kg/day (or cumulative dose >120 mg/kg) treatment, as compared to 39 to 82% with lower dosage treatment.[131]

Today, we recommend a 12-month treatment course of isotretinoin 0.5 to 1 mg/kg/day in most cases of severe acne, with a >150 mg/kg cumulative dose. Factors contributing to the need for longer treatment include a low dosage regimen (0.1 to 0.5 mg/kg/day), presence of severe acne lesions, extrafacial involvement and prolonged history of the disease.[132] Higher dosages are indicated particularly for severe involvement of the chest and back.[131]

Contraception is essential in women of childbearing age during isotretinoin treatment at all dosages.[133,134] Estrogens, antiandrogens and their combinations inhibit sebum production by 12.5 to 65%. A combination of isotretinoin with systemic corticosteroids is initially required in acne fulminans. In contrast to the opinion that isotretinoin may be a frequent precipitating factor, in a series of 24 patients with acne fulminans only 5 had received isotretinoin before the onset of the disease.[135]

5.3.3 Rosacea and Other Acne-Related Dermatoses

The efficacy of isotretinoin 0.4 to 1 mg/kg/day for 2 to 6 months in severe or recalcitrant rosacea has been well documented.[93,136-138] Marked regression of skin lesions and recession of concomitant erythema and oedema are seen within 4 to 8 weeks. The anti-inflammatory action of isotretinoin must be considered a a possible candidate mechanism for its efficacy in rosacea, since there is no evidence for a follicular disorder and sebum synthesis is normal.

Data on long term remissions in severe rosacea are contradictory; however, remissions of up to 2 years have been documented. The daytime use of a sunscreen is essential. In a recent randomised trial, low-dose systemic isotretinoin (10 mg/day) reduced inflammatory papules to 30% and erythema to 60% of baseline after 16 weeks of treatment. The effect lasted at least 16 weeks after drug withdrawal. Interestingly, topical tretinoin (0.025% cream at night) also reduced papules to 43% and erythema to 73% of baseline.[136]

Rhinophyma responds to systemic isotretinoin (0.5 to 1 mg/kg/day for 3 to 6 months), preferably at its early inflammatory stages. Improvement of early rhinophyma probably occurs because of diminution of the sebaceous glands, while fibrotic changes are resistant. Teleangiectasia responds only partially because of the recession of general inflammation. Rhinophyma treatment with isotretinoin 1 mg/kg/day for up to 18 weeks resulted in a 9 to 23% reduction of the nasal volume in 9 patients.[137]

Gram-negative folliculitis responds well to oral isotretinoin 0.5 to 1.0 mg/kg/day (in individual cases initially ≤2.0 mg/kg/day) for 8 to 24 weeks, and usually results in long term remissions. The efficacy of isotretinoin is probably a result of a reduction of the sebaceous gland volume, sebostasis and skin 'drying'; which impair the growth conditions of *Klebsiella*, *Enterobacter*, *Citrobacter*, *Escherichia coli* and *Pseudomonas aeruginosa* (Gram-negative folliculitis type I), as well as *Proteus mirabilis* (type II).

Acneiform dermatoses of the elderly, such as sebaceous gland hyperplasia, actinic elastosis with comedones formation (Favre-Racouchot disease), and demodex folliculitis can improve with long term treatment with isotretinoin 2.5 to 10 mg/day. Acne necroticans (isotretinoin 1 mg/kg/day for 5 weeks)[139] and recalcitrant oil acne (0.5 mg/kg/day for 12 weeks)[140] may respond to treatment, followed by long term remission, but halogen acne seems resistant.[141]

Preoperative isotretinoin treatment of inverse acne with 0.8 to 1 mg/kg/day for at least 4 weeks, reducing to 0.5 to 0.7 mg/kg/day for an additional 4- to 8-week period and 0.2 to 0.4 mg/kg/day as a maintenance or postoperative treatment has been recommended in some cases.[142] Surgical intervention is required in inverse acne; isotretinoin is

by itself, with rare exceptions, insufficient to stop the disease. In hidradenitis suppurative and steatocystoma multiplex suppurativum, the overall inflammation responds to isotretinoin but the non-inflammatory or cystic lesions remain relatively uninfluenced.

5.4 Retinoids in Skin Cancer

The exact mechanisms by which oral retinoids act beneficially in skin neoplasia and/or prevent skin cancer are still largely unknown, but promotion of terminal epithelial cell differentiation and induction of apoptosis may lead to tumour regression. Also, control of cell growth and cell differentiation may be mediated in part by interactions between different nuclear retinoid receptor species and the respective response elements of DNA. An alternative pathway by which retinoids can mediate signals is by interacting with the transcription factor AP-1. This complex of the 2 proto-oncogenes, *c-fos* and *c-jun*, plays a crucial role in cell cycle progression.[143] Recent results indicate that inhibition of the AP-1 complex by retinoids decreases the rate of cell proliferation.[65]

Recently, we demonstrated the significance of the sphingomyelin cycle as a growth and differentiation control mechanism in human skin.[144] This mechanism leads to elevation of intracellular ceramide levels and, as shown in haemopoietic cell lines, ceramides may represent a new second messenger, leading to inhibition of cell growth, induction of differentiation and apoptosis.[145] In this context, it may be of importance to note that retinoic acid was shown to elevate intracellular ceramide levels and that this elevation was paralleled by inhibition of cell proliferation.[146]

5.4.1 Prevention of Skin Cancer

Synthetic retinoids have been administered not only for therapy of skin malignancy, but also in several randomised chemoprevention trials. The data collected suggest that topical or oral administration of synthetic retinoids has a significant effect in reversing premalignant skin lesions and maintaining normal differentiation.[147-149]

Successful prevention of basal cell carcinomas and squamous cell carcinomas in patients with xeroderma pigmentosum has been described with oral isotretinoin[41] and oral etretinate.[150] Isotretinoin was shown to reduce the occurrence of basal cell carcinomas by 80% and of squamous cell carcinomas by 60% over a period of 2 years. Etretinate was seemingly more effective with respect to squamous cell carcinoma prevention, with a reduction rate of 75%.

Both retinoids have also been shown to be beneficial in preventing the appearance of cutaneous tumours in the nevoid basal cell carcinoma syndrome;[151] Goldberg et al.[152] concluded that isotretinoin 0.4 mg/kg/day is effective for chemoprevention in these patients. Etretinate 50 mg/day has been advocated for chemoprevention in renal transplant recipients with a more than 20-fold increased risk of developing skin cancer.[153] Transplant recipients show increased metastatic potential, leading to a 10-fold higher mortality rate from skin cancer. Therefore, the benefit of systemic retinoid therapy by etretinate 25 to 50 mg/day appears an important improvement in managing these patients. Recently, a combination of topical tretinoin and low-dose etretinate (10 mg/day) has been proposed for chemoprophylaxis,[154] also for reducing the adverse effects of oral medication.

5.4.2 Therapy of Precanceroses and Skin Cancer

Keratoses were the first skin alterations to be treated topically with tretinoin.[155] Treatment of actinic keratoses, bowenoid epithelial praecancerosis, etc., with various retinoids seems well established today. Successful chemoprevention of actinic keratoses with topical tretinoin has been described[156] and other authors have summarised and commented favourably on its beneficial effect. Systemic administration of etretinate has been also shown to reduce actinic keratoses by 90% but, overall, oral intake seemed inferior in comparison to topical treatment.[157]

Good results were obtained in the treatment of actinic keratoses using topical isotretinoin (0.1%); 40% of all facial lesions disappeared after 24 weeks.[152] Misiewicz et al.[159] compared a cream

containing arotinoid methylsulphone versus tretinoin cream in a double blind study, and found that the arotinoid compound was more effective in actinic keratoses and produced less local adverse effects.

Oral leucoplakia has been shown to be retinoid-sensitive (both etretinate and isotretinoin),[160,161] and good therapeutic results have been achieved; regressions between 61% (isotretinoin) and 92% (etretinate) have been reported.

Keratoacanthoma as a semimalignant tumour has been described to respond in nearly all patients under oral treatment with isotretinoin[162] or etretinate.[163] However, relapses may occur after therapy. As a rule, oral retinoids are not recommended as first line treatment for this condition, but postsurgical retinoid administration may prevent relapse in multiple tumours.

Basal cell carcinomas show minor response to oral retinoid treatment, even though some flattening may occur after several weeks or months. The retinoid effect is particularly unsatisfactory in nodular, ulcerous and/or sclerodermiform tumours which still show infiltrative growth.[164]

In contrast to the benefits of chemoprevention, no satisfactory therapeutic results have been obtained in squamous cell carcinomas either with etretinate or with isotretinoin monotherapy. Recently, however, effective combinations of isotretinoin with IFNα-2a were reported in patients with advanced squamous cell carcinomas. In a group of 34 patients, 8 complete and 14 partial remissions (65%) were observed.[165,166] Another trial with 13-*cis*-retinoic acid (1 mg/kg/day) and IFNα-2a (3 or 6 MU/day) produced benefit in 68% of the patients.[167]

5.4.3 Other Skin Neoplasms

Melanomas are not sensitive to retinoids. Monotherapy with isotretinoin, etretinate, tretinoin[168] and fenretinide[169] as well as combination of isotretinoin with IFNα-2a[167,170] have been shown to be ineffective in melanoma. Also, vitamin A does not seem to prevent neoplasia if used as an adjuvant.

Successful monotherapy of cutaneous T cell lymphoma has been early reported with etretinate, isotretinoin[171-175] and also with the potent arotinoid Ro 13-6298;[176] however, the combination of etretinate and PUVA appeared to be superior to retinoid alone. Jones and co-workers[177] successfully treated patients with mycosis fungoides and Sézary syndrome with etretinate (1 mg/kg/day) and electron beam therapy (35Gy), but this combination provided no additional benefit for the course of the disease.[177] Some synergistic effect was found with the combination of retinoids and chemotherapy in advanced mycosis fungoides.[172,173,178,179]

A new promising approach for oral treatment of cutaneous T cell lymphoma is the combined administration of etretinate and IFNα-2b[180-182] or IFNα-2a.[183] From the results obtained it may be concluded that IFNα-2b is more effective than IFNα-2a since the respective remission rates were 77% and 53%. Also, a good therapeutic effect was seen with isotretinoin and IFNα-2b (a remission rate of 57%).[184] Here again, it seems that retinoids and IFN may act synergistically: IFNs are thought to induce increased expression of RARs and, vice versa, retinoids may increase the expression of IFN receptors.

Von Roenn and coworkers[185] reported some beneficial effect of oral tretinoin in patients with HIV-related Kaposi's sarcoma. In a phase II study utilising tretinoin 100 mg/m^2/day they found stable disease in 2 of their 8 patients: an increased dosage (175 mg/m^2/day) was less effective. In another preliminary study in 7 patients (tretinoin 2 mg/kg/day) 3 partial remissions and 3 stable disease courses were obtained.[186] Possibly, systemic retinoids may inhibit or reduce endothelial proliferation *in vivo*, as they do *in vitro*.[85]

5.5 Miscellaneous Disorders

Oral retinoids have been used in other dermatoses. In particular, etretinate/acitretin were found effective in 3 entities of different pathogenetic background:

- in lichen planus,[187] including oral manifestations of lichen mucosae oris with papillomatous and erosive/bullous lesions;
- in cutaneous variants of lupus erythematosus (LE), particularly the hyperkeratotic lesions of chronic-discoid LE;
- in lichen sclerosus et atrophicus mostly localised in the anogenital area in women (kraurosis vulvae).

Sometimes, corticosteroids are used topically or systemically in addition, and oral retinoids are helpful for reducing their dose (e.g. in lichen planus, LE). The beneficial effect of retinoids in these entities underlines their immunomodulatory dermal action. Prurigo nodularis may be another entity responding well to oral retinoid treatment. The use of oral retinoids in bullous diseases, and also in pyoderma vegetans, Kyrle's disease etc., remains unsatisfactory. Some effect will be seen[188,189] in sarcoidosis or sarcoid granulomas and in granuloma annulare disseminatum, but randomised trials or case series reports are lacking.

6. Adverse Reactions and Tolerability

The adverse effect profile of oral retinoids is closely associated with hypervitaminosis A.[21] It includes a characteristic mucocutaneous symptomatology, alopecia, elevation of serum triglycerides, hyperostosis and extraskeletal calcification. Retinoids are highly teratogenic if given orally during embryogenesis.

Because of these adverse effects, several contraindications for retinoid treatment should be considered and careful clinical monitoring is necessary. Oral retinoid treatment appears today strictly contraindicated in pregnancy, the lactation period and in severe hepatic and renal dysfunction;[190,191] hyperlipidaemia, diabetes mellitus and severe osteoporosis are relative contraindications. Administration of retinoids with diet or lipid lowering agents is possible in cases of slightly increased serum lipids.[192] Co-medication with vitamin A (increased toxicity), tetracyclines (cranial hypertension) and high doses of aspirin (potentiation of mucosal damage) should be avoided.

If retinoid therapy is necessary in women of childbearing age, pregnancy tests have to be performed before and during treatment. Oral contraceptives are recommended, since the common retinoids used do not interfere with the antiovulatory activity even after prolonged intake.[107] Before administering the drug it is strictly recommended that the risk of foetal malformations is explained, and information inserts should be signed prior to treatment by women of child bearing age. Despite some experimental and animal data that retinoids may influence spermatogenesis, no impairment of male reproductive capacity in men has been documented. In a recent case report it was assumed that ejaculatory failure may occur with isotretinoin.[193]

6.1 Mucocutaneous Adverse Effects

The mucocutaneous adverse effects of oral retinoid treatment are well known but are mostly tolerable, if the drug is administered (a) in the proper indications, (b) at the appropriate dose-level, and (c) under careful monitoring by the physician.

Adverse effects include skin and mucosal dryness (xerosis, cheilitis, conjunctivitis, urethritis), skin fragility and/or stickiness, retinoid dermatitis, palmoplantar desquamation, pruritus and hair loss. Nearly all these symptoms are dose-dependent in incidence and severity, and are fully reversible on reducing the daily dose or on drug withdrawal.

Their incidence rates may slightly differ depending on the type of retinoid given and the initial dose used. In our 25 years of clinical experience with oral retinoid therapy, only severe abrupt hair loss may require drug withdrawal in rare instances. Since the frequency of cheilitis is nearly 100%, its appearance 2 to 3 weeks after initiation of treatment is regarded by us as a marker of sufficient absorption. In patients receiving 0.5 to 1.0 mg/kg/day with a lack of or insufficient clinical response to therapy, and who have not experienced mucocutaneous adverse effects (non-responders), we recommend blood concentration monitoring to ensure absorption (see section 7.2).

6.2 Eye Symptomatology and Pseudotumour Cerebri

With or without conjunctivitis, eye dryness may cause considerable discomfort in patients wearing contact lenses, and requires administration of artificial tears. Hemeralopia may occur, possibly because of some interference of retinoids with 11-*cis*-retinaldehyde formation. Also, papillary oedema, corneal abnormalities with opacities and cataract, transient acute myopia and abnormal electroretinograms have been described with retinoid treatment. In some instances, they may require ophthalmological consultation.

Pseudotumour cerebri was initially documented in patients receiving higher dosages of isotretinoin (≥1 mg/kg/day), particularly in combination with tetracyclines. No further reports were published with etretinate/acitretin in recommended dosages, but papilloedema should be considered in patients with pre-existing intraocular hypertension or glaucoma.

6.3 Serum Lipids and Liver Function

Hyperlipidaemia occurs more often with increased serum triglycerides (20 to 40%) than with cholesterol increase (10 to 30%).[194,195] It is possible that retinoids enhance lipoprotein synthesis, decreasing elimination of blood lipids. They may also slightly increase synthesis of lipids. Increased apolipoprotein B and to a lesser extent increased total apolipoprotein A under retinoid treatment support the former hypothesis.

The influence on serum triglyceride and cholesterol levels is proportional to the dose and reverses within 4 to 8 weeks after discontinuation of treatment.[196] Hyperlipidaemia leads to cessation of treatment in <5% of patients.[195] Hyperlipidaemia is likely to occur in patients with predisposing factors such as obesity, alcoholism, nicotine abuse, diabetes mellitus, familial hyperlipidaemia, and users of β-blockers, contraceptives and thiazides.[93]

The greatest increase in triglycerides is associated with the very low density lipoprotein fraction (VLDL; with isotretinoin and etretinate) and in cholesterol with the low density lipoprotein (LDL) fraction (isotretinoin) and the VLDL and/or LDL fractions (etretinate), with a parallel decrease of the high density lipoprotein (HDL) fraction.[197]

Hyperlipidaemia during retinoid treatment can be partially managed by an appropriate diet low in fat. A high fish oil diet was found effective in partially reducing hypertriglyceridaemia (27%) and increasing HDL cholesterol (11%) in patients treated with etretinate or acitretin.[198] Lipid-lowering drugs taken orally are also effective, if required.

Synthetic retinoids have much less affinity for the liver than vitamin A. Most reported retinoid-induced hepatotoxic reactions have occurred with etretinate treatment, probably because of its high tissue-to-blood ratio, but isotretinoin may also be associated with such reactions.[194] Elevations of liver enzymes have been documented in 20 to 30% of patients usually within 0.5 to 2 months of commencing therapy, but marked alterations are infrequent.[196] Chronic toxicity resulting from retinoid treatment is a rare event, and long term etretinate treatment is not associated with increased liver toxicity, despite the fact that cases of biopsy-proven hepatitis have been documented.[191]

6.4 Bone Changes

Changes in bone formation are a well recognised, common adverse reaction seen in chronic vitamin A intoxication.[9,199,200] These changes include hyperostosis, periostosis, demineralisation, thinning of the bones, and premature closure of the epiphyses. Short term retinoid therapy (≤2 years) in children seems to be well tolerated. Data concerning long term retinoid treatment are conflicting. Recent studies of etretinate treatment in large series of children and adolescents at an initial dosage of 1 mg/kg/day for ≤11 years did not register significant bone abnormalities,[201-203] disputing earlier case reports which suggested chronic bone toxicity in children.

Bone abnormalities in children, particularly premature closure of the epiphyses, are indeed as-

sociated with high retinoid doses (>1 mg/kg/day), vitamin A supplementation, and treatment for more than 5 years. Should bone abnormalities occur, they may not resolve upon cessation of treatment. In adult patients, chronic retinoid toxicity confined to bones is commonly assumed to be caused by isotretinoin rather than acitretin/etretinate.

The effects of acitretin on the skeletal system are not yet well documented; however, available data suggest similarities to etretinate.[106] In a large prospective study, Tangrea et al.[204] used very low doses of isotretinoin (0.14 mg/kg) compared with placebo for 3 years in the prevention of basal cell carcinoma. They found radiographic evidence for significant progression of pre-existing hyperostotic anomalies (40% with isotretinoin *vs* 18% with placebo).

High-dose isotretinoin for ≥2 years seems to induce skeletal hyperostoses and anterior spinal ligament calcification, similar to those seen in diffuse idiopathic skeletal hyperostosis (DISH). Changes occur in cervical spine more often than in the thoracic and lumbar spine. Some patients have shown extraspinal calcification (ankles, pelvis, knees). Small asymptomatic changes can be detected as early as after 1 year of treatment. Long term etretinate treatment was known to induce extraspinal tendon and ligament calcification and DISH-like involvement. In a further study, 5% of patients treated with acitretin for 1 to 2 years presented with bone changes. While a definite relationship between hyperostoses and cumulative dosage of isotretinoin could not be established, they are likely to occur at a cumulative etretinate dose of >30g.[205]

Osteoporosis seems to be a toxic effect of long term etretinate but not isotretinoin therapy.[206] In addition, bone pain and acute arthritis have been rarely documented.[9,207] Since about 50% of patients with skeletal bone changes are asymptomatic, a single radiograph of the ankle, being the most common site of involvement, is a reasonable test before treatment and then repeated yearly with long term and/or high-dose retinoid treatment. In addition, growth measurements are required in children.

6.5 Arthralgias and Myalgias

Arthralgias and myalgias may occur in up to 2 to 5% of individuals receiving oral retinoids >0.5 mg/kg/day, with or without calcification of ligaments. Their appearance seems more common in adolescents and young adults, particularly those treated with isotretinoin. In some cases, severe muscle pain and temporary disability with early morning arthralgias were seen. Occasionally, concomitant malaise and fever may occur, and increases of serum enzymes including creatine phosphokinase have been found. In some rare cases 'retinoid hypersensitivity reaction' with myoarthralgias has been suspected.

6.6 Teratogenicity

All known biologically active retinoids are highly teratogenic, both in animal experiments and in humans.[133,208-211] Their biological action, beneficial for skin disease, seems related to the teratogenic risk, and is particularly high for women exposed to treatment during the first trimester of pregnancy. The indiscriminate transfer of retinoids through the placenta leads to similar concentrations of the drug and its isomers both on the maternal and the fetal site.[26] Therefore, systemic teratogenicity of retinoids has remained the major concern today and for future retinoid research.

The clinical pattern of abnormalities induced by retinoids is rather characteristic, although some similarities to other teratogenic drugs such as methotrexate may occur. They induce:

- CNS and craniofacial abnormalities with internal ear and eye malformations and facial dysmorphia;
- bone abnormalities with skeletal malformations; occasionally leading to limb defects;
- cardiovascular disorders.

All three are major birth defect phenotypes, in some cases with lethal outcome. In addition, general retardation, thymus hormone abnormalities, parathyroid hormone deficiency, colobomas, choa-

nal atresia, etc., have been described. There are some differences of malformation pattern that may characterise the influence of retinoic acid on the one hand and etretinate/acitretin on the other, but these remain without major clinical relevance.

Today, all known therapeutic schedules with retinoids are regarded as potentially teratogenic. Even though topical treatment with tretinoin/isotretinoin has been previously regarded as 'safe', recent observations after the use of tretinoin cream have raised considerable concern.[212-214]

After topical application of isotretinoin (0.05%) in hairless rats the plasma concentrations of isotretinoin and its metabolites were below the detection limit.[134] Nevertheless, all investigators agree today that the topical application of retinoids should be strictly avoided during the first trimester of pregnancy. Since November 1 1994, topical application of 0.05% tretinoin cream/0.05% isotretinoin gel is not permitted during the entire period of pregnancy in Germany, according to a decision of the Federal Drug Commission.

Concerning systemic administration, it has been known that a single oral retinoid dose of 25mg given in pregnancy during the time period of organogenesis (4 to 6 weeks) may be associated with embryonic malformations,[215] whereas oral retinoids taken during late in pregnancy did not influence the embryo. Despite this difference indicating a time-related teratogenic risk,[216] all present recommendations require avoidance of any oral administration of isotretinoin, etretinate or acitretin over the entire period of pregnancy.

The minimal dose of circulating retinoids associated with teratogenicity is not sufficiently known. The detection limit by using the reverse phase high performance liquid chromatography (HPLC) technique is regarded as the major parameter, and unmeasurable concentrations of <2 μg/L may be regarded as nonteratogenic. In this respect, some authors have pointed out that endogenous retinoic acid levels may be 2 to 4 μg/L.

Based on pharmacokinetic data, current guidelines include the use of contraception 1 month before initiation of oral treatment with isotretinoin and etretinate/acitretin and continuation of contraception for 1 to 2 months after isotretinoin and 2 years after etretinate/acitretin treatment.[217-219] A negative pregnancy test is required in all young women considered for treatment 2 weeks before initiation of treatment and at day 2 or 3 of a normal menstrual cycle.

7. Clinical Monitoring

Oral retinoid treatment requires clinical experience and regular monitoring. Retinoids are not the 'easy' drug for the 'difficult' patient. Initial high-dose retinoid therapy may cause physical discomfort, and the large number of undesired potential adverse reactions to be discussed and explained during the first consultation may limit the enthusiasm of the individual to give his/her consent for treatment.

7.1 Monitoring of Clinical and Laboratory Parameters

Today, clinical monitoring requires physical examination every 4 weeks to manage mucocutaneous adverse effects and to ensure compliance. After administration of isotretinoin and also etretinate/acitretin, elevations of blood sedimentation rate, transaminases (ALT, AST, γ-glutamyl transferase), plasma urea and serum lipid levels may occur. Liver enzymes (transaminases, alkaline phosphatase, γ-glutamyl transferase), serum creatinine and blood glucose should be measured every 4 to 8 weeks. If elevations appear, the retinoid dose given should be reduced by 50% or be interrupted.

Elevations of serum lipids and, more rarely, of cholesterol, were shown early to be occasional adverse effects of oral retinoids.[12,97,188,194,220] Such elevations are more often seen in older patients, particularly in those with familial predisposition or other risk factors such as diabetes, obesity, heavy smoking, hypertension, oral contraceptives and corticosteroids. Furthermore, it was shown that the amounts of creatine kinase, apolipoprotein B, total cholesterol and LDL cholesterol increased significantly during therapy with isotretinoin.[221] Triglyceride and cholesterol levels have to be moni-

tored every 4 weeks over a period of 2 to 3 months during the initial phase (12 hours after intake of food) and later on every 8 weeks. Selection of patients and appropriate diet schedules are recommended as necessary precautions for reducing the risk of hyperlipidaemia.

Prior long term therapy with oral retinoids, e.g. in disorders of keratinisation,[93,117] x-rays of the spine and the long bones should be taken, particularly in adolescents and in young adults. There are no established regulations for the time intervals of skeletal monitoring: the decision should be taken separately for each patient. Particularly in children and adolescents, regular radiological examinations of the skeletal system and the epiphyseal cartilage of tubular bones and measurements of general growth are necessary.[222]

7.2 Monitoring of Retinoid Bioavailability and Body Storage

Monitoring of retinoid blood concentrations during and after oral retinoid therapy remains of major importance for managing cases of non-responders or considering recommendations for pregnancy. In some patients showing little clinical response the retinoid blood concentrations have been extremely low, and only an increase in dosage up to 1.5 mg/kg/day was followed by target blood concentrations and sufficient clinical response.[223]

HPLC is the method of choice for highly sensitive and selective retinoid detection and measurements.[224-226] Following simultaneous extraction with organic solvent, the compounds can be measured by normal or reverse-phase HPLC,[5,227] with a detection limit of approximately 4 µg/L in plasma. Using a system of column-switching HPLC the limit for measurement can be reduced to 2 µg/L.[228]

If traces of retinoids are detected in the blood of pregnant women, interruption of pregnancy is recommended. In a few cases, traces of etretinate and acitretin were detected 9 to 18 months after drug withdrawal.[217,219] It is assumed that plasma levels of isotretinoin below the detection limit of 2 µg/L are not teratogenic because the naturally occurring 13-*cis*-retinoic acid reaches levels between 1.0 and 2.2 µg/L under fasting conditions.[71] In the absence of these predictors in blood, however, the presence of retinoid traces in tissue is not fully excluded.

When plasma concentrations of etretinate are below the detection limit, etretinate and 13-*cis*-acitretin can be monitored in subcutaneous tissue. The prevalence of detectable etretinate concentrations in subcutaneous tissue was found to be higher (83%) than in plasma (45%), both among current acitretin users and also among those who had stopped acitretin therapy.[229] Since traces of 13-*cis*-acitretin were found in fat up to 29 months after cessation of treatment, it has been suggested that the recommended contraception period of 2 years should be reconsidered.

8. Topical Treatment with Retinoids

Topical application of retinoids avoids their considerable systemic toxicity and has led to widespread use of these compounds, especially of tretinoin, e.g. for acne vulgaris, photodamage and also for actinic keratoses.[230,231]

8.1 Pharmacokinetics

Topical application of tretinoin is followed by partial isomerisation to 9-*cis*-retinoic acid and isotretinoin, and to numerous other metabolites within the epidermis.[232] Approximately 80% of the drug remains on the skin surface, while its penetration through both the stratum corneum and the hair follicles is vehicle dependent.[233] The initial diffusion into the intact stratum corneum occurs rapidly, within a few minutes.[234] Further diffusion into the epidermis and subsequently the dermis proceeds more slowly.[235]

Tretinoin induces the activity of cytochrome P450 retinoic acid-4-hydroxylase in the keratinocytes, which converts tretinoin to its inactive metabolite 4-hydroxy-retinoic acid.[236]

The cellular retinoic acid binding protein-II (CRABP-II), initially proposed to transport retinoic acid to its nuclear receptors, is the predominant form of CRABP in human skin, found in both keratinocytes and fibroblasts.[237] Topical applica-

tion of tretinoin up-regulates CRABP-II, whose exact function remains unclear.[238] The facts that highly homologous proteins are found in all animal species and that a RARE has been identified within the promoter region of the CRABP-II gene suggest that either CRABP-II regulates the bioavailability of retinoids by reducing the free levels available to bind to the specific nuclear receptors, or acts as a co-factor in retinoid metabolism.[52]

Topical isotretinoin probably also exhibits anti-inflammatory activity as it was shown to significantly inhibit the leukotriene B_4–induced migration of neutrophils in 16 healthy volunteers.[91] Interestingly, tretinoin, arotinoid methyl sulphone and arotinoid ethyl sulphone were inactive in this study.

Acitretin has been detected in the skin after topical application, whereas concentrations in the skin after a single 24-hour topical application of a saturated acitretin-isopropylmyristate formulation were comparable to those after systemic application in a steady-state situation.[239] However, topical acitretin was practically ineffective in psoriasis and disorders of keratinisation.

8.2 Clinical Applications of Topical Retinoids

8.2.1 Acne Vulgaris

Topical tretinoin and isotretinoin are effective comedolytic agents.[17,18] They normalise desquamation of the follicular epithelium, promote drainage of preexisting comedones, and inhibit the formation of new comedones and other lesions.[240,241] The restored follicular environment impedes the growth of *P. acnes* and minimises the rupturing of comedones into surrounding tissue.

The efficacy of topical isotretinoin 0.05% gel versus vehicle for 14 weeks was examined in a randomised study of 268 patients with acne.[17] Isotretinoin significantly reduced the inflammatory lesions after 5 weeks and the noninflammatory lesions after 8 weeks, compared with the vehicle. In another double-blind randomised study involving 77 patients, isotretinoin gel was compared with benzoyl peroxide gel 5% and vehicle.[18] Benzoyl peroxide had a more rapid effect on inflammatory lesions, but both active treatments were efficacious. A new retinoid, adapalene, has been recently introduced for the topical treatment of acne vulgaris, possibly showing better tolerability than tretinoin (see section 9).

Topical retinoids are regarded today as first-line treatment for both noninflammatory and also inflammatory forms of acne. Substantial clinical improvement is apparent after 6 weeks, with maximal improvement occurring in 3 to 4 months. Long lasting remissions can be maintained with continued application on an infrequent, but regular basis. Topical retinoids may heighten susceptibility to sunlight, and the use of sunscreens is recommended.

Since topical retinoids normalise desquamation of the follicular epithelium and topical antibiotics and antimicrobials inhibit *P. acnes*, neutrophil chemotaxis and the production of free fatty acids, the concomitant use of a retinoid with an antimicrobial agent addresses 3 of the 4 pathogenic factors of acne. Combination therapies utilising retinoids and antimicrobial/antibiotic agents should be sequential, i.e. the antimicrobial/antibiotic preparation being applied in the morning, and the retinoid preferably administered at night.

8.2.2 Photoaging and Aging

Well controlled studies attest to the efficacy of topical tretinoin and isotretinoin in improving the features of photoaging.[242-246] Retinoids induce epidermal hyperproliferation, compaction of stratum corneum, deposition of glycosaminoglycans in the epidermis and of collagen in the immediate subepidermal region, and slow the rate of collagen breakdown by reducing collagenase levels and by promoting the production of collagenase inhibitors.[247,248] Epidermal melanin is reduced because of a decrease in the rate of melanosomes transferred from melanocytes to keratinocytes secondary to the increase in epidermal proliferation.

Daily application of 0.1% tretinoin cream leads to significant improvement of wrinkling and hyperpigmentation in 16 weeks.[246] A 0.05% tretinoin emollient cream applied daily for 24 weeks was also shown to be effective on fine wrin-

kling, mottled hyperpigmentation, and roughness of the skin, as compared to placebo in a double-blind, randomised trial in 296 patients.[243]

A lower tretinoin dose, 0.025% cream, has been recently shown to be as effective as tretinoin 0.1%, and induced a lower degree of irritation.[242] Combination of 0.1% tretinoin cream with 0.05% diflorasone diacetate cream for 16 weeks once daily induced striking clinical improvement in wrinkling and caused bleaching in 5 postmenopausal women with severe photoaging changes.[249] Tretinoin 0.025% was also able to substantially alter the involutional structural changes in intrinsically aged sun-protected skin of 6 elderly women treated once daily for 9 months.[250]

8.2.3 Disorders of Pigmentation

Epidermal melasma responds to topical tretinoin, either alone or in combination with hydroquinone and hydrocortisone, in conjunction with a broad-spectrum sunscreen.[251] Epidermal melanin is reduced by retinoic acid. Possible mechanisms include reduction in the transfer rate of melanosomes to keratinocytes and inhibition of tyrosinase activity leading to reduction of melanogenesis.[252]

8.2.4 Other Indications

Clinical trials have confirmed the beneficial effect of topical tretinoin and established the efficacy of isotretinoin 0.1% applied twice daily for 24 weeks in the treatment of actinic keratoses.[158,253] Plane warts in children, especially on the face, responded well to 6-week treatment with tretinoin 0.05% once daily as shown in a randomised study in 50 children.[254] Also, actinic cheilitis responds well to long term treatment with tretinoin 0.1% gel once or twice daily.[255] Early stretch marks were found to improve after tretinoin 0.1% cream once daily for 6 months in a double-blind, randomised, vehicle-controlled study involving 22 patients.[256]

8.2.5 Adverse Effects of Topical Retinoids

It is well known that topical application of retinoids causes a dose-dependent dermatitis with erythema, peeling, dryness and pruritus.[242,243,245] These effects tend to peak within the first month of treatment and diminish thereafter. Although no evidence exists for embryotoxicity and teratogenicity of topical retinoids in humans, even after continued application over several years,[213,257,258] treatment has to be interrupted if the patient becomes pregnant (see also section 6.6).

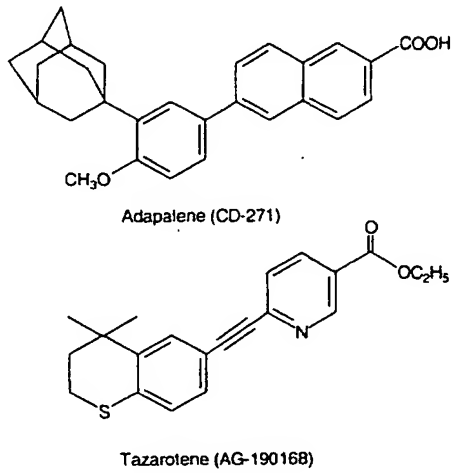

Fig. 3. Adapalene and tazarotene.

9. New Trends and Outlook for the Future

Most known retinoids initiate a series of biological responses by indiscriminate binding to and/or by activation of several regulatory receptors, both of cytosolic or nuclear localisation. Nevertheless, in spite of the tremendous increase of knowledge on the field, it still remains unclear how transcription of activated genes influences the various retinoid-responsive skin disorders and what the biological significance of the receptor binding is.

Retinoids do not necessarily act by influencing nuclear receptors; it is conceivable that their therapeutic effect is mediated by cell membrane mechanisms or direct pharmacologic action. Nevertheless, further development of receptor-selective retinoid ligands could contribute to better discrimination of their activity either towards keratinising epithelia or to the sebaceous gland, and also help

to enlarge their therapeutic window by minimising adverse effects.

Receptor-selective retinoid agonists and/or antagonists are now the subject of ongoing research, and new, more receptor- and disease-specific retinoids may be discovered in the near future. Recently, oral tretinoin (45 mg/m^2/day) has been introduced for the treatment of acute promyelocytic leukaemia. In dermatology, two new arotinoids have been developed for topical use in skin disease, adapalene and tazarotene (fig. 3), and more synthetic compounds may follow (table VII).

Adapalene[13,14,19] is a new naphthoic acid arotinoid with high chemical and physical (light) stability and lipophilic properties. The drug has comedolytic and anti-inflammatory action. It does not bind to CRABP,[259] although it enhances its synthesis, and its receptor selectivity appears to be RARβ > RARγ >> RARα. The drug is topically effective in acne and has also mild antipsoriatic properties.[262] In acne, adapalene was found in randomised studies with 0.1% gel preparations to be better or at least equal to 0.025% tretinoin in reducing total or noninflammatory lesions after 12 weeks of treatment.[19] Local irritation occurs, however, in about 50% of patients, which may limit its long term value. Adapalene has been recently introduced in several european countries as a topical antiacne preparation. Transdermal absorption is very low and the teratogenic risk after topical application appears minimal; however, we do not recommend its use during pregnancy.

Tazarotene[15] is an acetylenic retinoid of the third generation. It is a poorly absorbed, nonisomerisable arotinoid which is rapidly metabolised to its free carboxylic acid, tazarotenic acid. The latter binds to RARβ > RARγ >> RARα, without any affinity for RXRs. It was found to normalise acanthosis with a decrease of hyperproliferative keratins CK 6/CK 16, decrease ECF receptor expression, restore normal expression and distribution of transglutaminase K, and increase filaggrin synthesis in the upper psoriatic epidermis, with low potential for systemic adverse effects. It has mild anti-inflammatory properties but is also an irritant in high topical doses.

Table VII. New retinoid compounds

Retinoid	Remarks
LGD-1069	RXR panagonist; currently in clinical trials
CD-1599	Chemical and tissue stability, probably less toxic effects
Tamibarotene (Am-80)	Studied as topical antipsoriatic agent in clinical trials
CD-437 (AHPN)	Induction of apoptosis
CD-2398	Up-regulates AP-1 complex, does not bind to RARs; currently in clinical anticancer trials
Ro 23-6457	Immunosuppressive properties
Mofarotene (Ro 40-8757)	Used in chemotherapy; enhances the activity of doxorubicin, cyclophosphamide, fluorouracil, interleukins

Abbreviations: RAR = retinoic acid receptor; RXR = retinoid X receptor.

Tazarotene has just been released in Germany and will be soon released in some other European countries and in the USA/Canada as a topical antipsoriatic agent (0.05 to 0.1 % gel). Clinical responses are seen after 2 weeks, with significant clearing after 6 to 12 weeks of treatment. Combination of tazarotene with less potent corticosteroids may increase the overall therapeutic potential and reduce local irritation, as shown by us at the beginning of the retinoid era.[203]

In the future, the group of arotinoids which we first introduced for the treatment of skin disease[260,261] appears promising for consideration as potential anticancer drugs. Better knowledge of the retinoid-induced intracellular events is needed. The next decade will allow further elucidation of how retinoids work and how cell dedifferentiation could be reversed under retinoid supervision.

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